

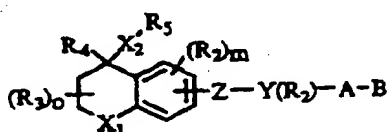
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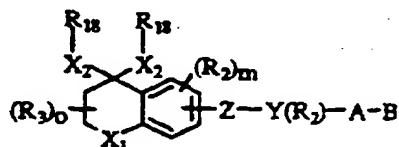
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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|--|-------------------------|------------|---|----|------------|-------------------------|----|------------|-------------------------|----|------------|-------------------------|----|------------|-------------------------|----|------------|-------------------------|----|---|--|
| (51) International Patent Classification <sup>6</sup> :<br>C07C 69/587, A61K 31/19, C07C 69/78,<br>245/10, A61K 31/655, C07C 235/66,<br>C07D 309/12, A61K 31/35  |                         | A2         | (11) International Publication Number: <b>WO 97/48672</b><br>(43) International Publication Date: 24 December 1997 (24.12.97) |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |   |  |
| (21) International Application Number: PCT/US97/10725<br>(22) International Filing Date: 19 June 1997 (19.06.97)<br>(30) Priority Data:<br><table border="0"> <tr> <td>08/667,664</td> <td>21 June 1996 (21.06.96)</td> <td>US</td> </tr> <tr> <td>08/667,666</td> <td>21 June 1996 (21.06.96)</td> <td>US</td> </tr> <tr> <td>08/667,665</td> <td>21 June 1996 (21.06.96)</td> <td>US</td> </tr> <tr> <td>08/667,215</td> <td>21 June 1996 (21.06.96)</td> <td>US</td> </tr> <tr> <td>08/667,216</td> <td>21 June 1996 (21.06.96)</td> <td>US</td> </tr> <tr> <td>08/667,663</td> <td>21 June 1996 (21.06.96)</td> <td>US</td> </tr> </table> |                         | 08/667,664 | 21 June 1996 (21.06.96)   | US | 08/667,666 | 21 June 1996 (21.06.96) | US | 08/667,665 | 21 June 1996 (21.06.96) | US | 08/667,215 | 21 June 1996 (21.06.96) | US | 08/667,216 | 21 June 1996 (21.06.96) | US | 08/667,663 | 21 June 1996 (21.06.96) | US | (72) Inventors: VULIGONDA, Vidyasagar, 15 Sweet Rain, Irvine, CA 92714 (US). TENG, Min; 2 Dove Street, Aliso Viejo, CA 92656 (US). BEARD, Richard, L.; 2341 Azure Avenue, Newport Beach, CA 92660 (US). JOHNSON, Alan, T.; 7 Via Arribo, Rancho Santa Margarita, CA 92688 (US). LIN, Yuan; 214 North Goldenrod Drive, Walnut, CA 91789 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US). SONG, Tae, K.; 3768 North Country Club Drive, Long Beach, CA 90807 (US). WONG, Harold, N.; 2 Ceramica, Rancho Santa Margarita, CA 92688 (US). DUONG, Tien, T.; Apartment 15C, 13 Bearpaw, Irvine, CA 92714 (US). GILLET, Samuel, J.; 6125 Hillmont Drive, Oakland, CA 94605 (US).<br>(74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, T-22-E, P.O. Box 19534, Irvine, CA 92623-9534 (US).<br>(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br>Published<br>Without international search report and to be republished upon receipt of that report. |  |
| 08/667,664   | 21 June 1996 (21.06.96) | US         |   |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |   |  |
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| 08/667,215   | 21 June 1996 (21.06.96) | US         |   |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |   |  |
| 08/667,216   | 21 June 1996 (21.06.96) | US         |   |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |   |  |
| 08/667,663   | 21 June 1996 (21.06.96) | US         |   |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |            |                         |    |   |  |
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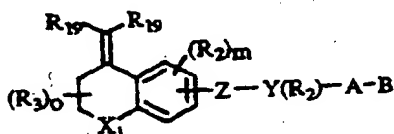
(54) Title: SUBSTITUTED TETRAHYDRONAPHTHALENE AND DIHYDRONAPHTHALENE DERIVATIVES HAVING RETINOID AND/OR RETINOID ANTAGONIST-LIKE BIOLOGICAL ACTIVITY



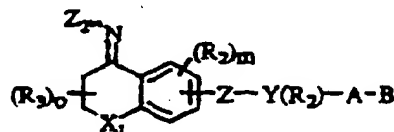
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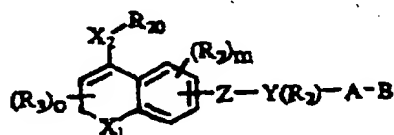
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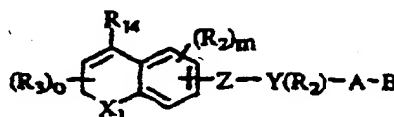
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(5)



(6)

(57) Abstract

Compounds of formulas (1-6) where the symbols have the meaning described in the specification, have retinoid and/or retinoid antagonist-like biological activity.

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1           SUBSTITUTED TETRAHYDRONAPHTHALENE AND  
2   DIHYDRONAPHTHALENE DERIVATIVES HAVING RETINOID  
3   AND/OR RETINOID ANTAGONIST-LIKE BIOLOGICAL ACTIVITY

4           1.   Field of the Invention

5           The present invention relates to novel compounds having retinoid  
6   and/or retinoid antagonist-like biological activity. More specifically, the  
7   present invention relates to substituted tetrahydronaphthalene and  
8   dihydronaphthalene derivatives which bind to retinoid receptors and  
9   have retinoid-like or retinoid antagonist-like biological activity.

10          2.   Background Art

11          Compounds which have retinoid-like activity are well  
12   known in the art, and are described in numerous United States and  
13   other patents and in scientific publications. It is generally known and  
14   accepted in the art that retinoid-like activity is useful for treating  
15   animals of the mammalian species, including humans, for curing or  
16   alleviating the symptoms and conditions of numerous diseases and  
17   conditions. In other words, it is generally accepted in the art that  
18   pharmaceutical compositions having a retinoid-like compound or  
19   compounds as the active ingredient are useful as regulators of cell  
20   proliferation and differentiation, and particularly as agents for treating  
21   skin-related diseases, including, actinic keratoses, arsenic keratoses,  
22   inflammatory and non-inflammatory acne, psoriasis, ichthyoses and  
23   other keratinization and hyperproliferative disorders of the skin,  
24   eczema, atopic dermatitis, Darriers disease, lichen planus, prevention  
25   and reversal of glucocorticoid damage (steroid atrophy), as a topical  
26   anti-microbial, as skin anti-pigmentation agents and to treat and reverse  
27   the effects of age and photo damage to the skin. Retinoid compounds  
28   are also useful for the prevention and treatment of cancerous and  
29   precancerous conditions, including, premalignant and malignant  
30   hyperproliferative diseases such as cancers of the breast, skin, prostate,  
31   cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral

1 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,  
2 leukoplakias and papillomas of the mucous membranes and in the  
3 treatment of Kaposi's sarcoma. In addition, retinoid compounds can be  
4 used as agents to treat diseases of the eye, including, without limitation,  
5 proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and  
6 other corneopathies, as well as in the treatment and prevention of  
7 various cardiovascular diseases, including, without limitation, diseases  
8 associated with lipid metabolism such as dyslipidemias, prevention of  
9 post-angioplasty restenosis and as an agent to increase the level of  
10 circulating tissue plasminogen activator (TPA). Other uses for retinoid  
11 compounds include the prevention and treatment of conditions and  
12 diseases associated with human papilloma virus (HPV), including warts  
13 and genital warts, various inflammatory diseases such as pulmonary  
14 fibrosis, ileitis, colitis and Krohn's disease, neurodegenerative diseases  
15 such as Alzheimer's disease, Parkinson's disease and stroke, improper  
16 pituitary function, including insufficient production of growth hormone,  
17 modulation of apoptosis, including both the induction of apoptosis and  
18 inhibition of T-Cell activated apoptosis, restoration of hair growth,  
19 including combination therapies with the present compounds and other  
20 agents such as Minoxidil<sup>R</sup>, diseases associated with the immune system,  
21 including use of the present compounds as immunosuppressants and  
22 immunostimulants, modulation of organ transplant rejection and  
23 facilitation of wound healing, including modulation of chelosis.

24 United States Patent Nos. 4,740,519 (Shroot et al.),  
25 4,826,969 (Maignan et al.), 4,326,055 (Loeliger et al.), 5,130,335  
26 (Chandraratna et al.), 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna  
27 et al.), 5,324,840 (Chandraratna), 5,344,959 (Chandraratna), 5,130,335  
28 (Chandraratna et al.), Published European Patent Application Nos. 0  
29 176 034 A (Wuest et al.), 0 350 846 A (Klaus et al.), 0 176 032 A  
30 (Frickel et al.), 0 176 033 A (Frickel et al.), 0 253 302 A (Klaus et al.),  
31 0 303 915 A (Bryce et al.), UK Patent Application GB 2190378 A



1 (Klaus et al.), German Patent Application Nos. DE 3715955 A1 (Klaus  
2 et al.), DE 3602473 A1 (Wuest et al., and the articles J. Amer. Acad.  
3 Derm. 15: 756 - 764 (1986) (Sporn et al.), Chem. Pharm. Bull. 33:  
4 404-407 (1985) (Shudo et al.), J. Med Chem. 1988 31, 2182 - 2192  
5 (Kagechika et al.), Chemistry and Biology of Synthetic Retinoids CRC  
6 Press Inc. 1990 p 334 - 335, 354 (Dawson et al.), describe or relate to  
7 compounds which include a tetrahydronaphthyl moiety and have  
8 retinoid-like or related biological activity. United States Patent No.  
9 4,391,731 (Boller et al.) describes tetrahydronaphthalene derivatives  
10 which are useful in liquid crystal compositions.

11 Published European Patent application Nos. 0 661 259 A1 and 0  
12 661 261 A1 (Bristol-Myers Squibb) describe further dihydronaphthalene  
13 and naphthalene derivatives which are said in the disclosures to have  
14 retinoid-like biological activity.

15 United States Patent Nos. 4,980,369, 5,006,550, 5,015,658,  
16 5,045,551, 5,089,509, 5,134,159, 5,162,546, 5,234,926, 5,248,777,  
17 5,264,578, 5,272,156, 5,278,318, 5,324,744, 5,346,895, 5,346,915,  
18 5,348,972, 5,348,975, 5,380,877, 5,399,561, 5,407,937, (assigned to the  
19 same assignee as the present application) and patents and publications  
20 cited therein, describe or relate to chroman, thiochroman and  
21 1,2,3,4-tetrahydroquinoline derivatives which have retinoid-like  
22 biological activity. Still further, several co-pending applications and  
23 recently issued patents which are assigned to the assignee of the present  
24 application, are directed to further compounds having retinoid-like  
25 activity.

26 Although pharmaceutical compositions containing retinoids have  
27 well established utility (as is demonstrated by the foregoing citation of  
28 patents and publications from the voluminous literature devoted to this  
29 subject) retinoids also cause a number of undesired side effects at  
30 therapeutic dose levels, including headache, teratogenesis,  
31 mucocutaneous toxicity, musculoskeletal toxicity, dyslipidemias, skin

1 irritation, headache and hepatotoxicity. These side effects limit the  
2 acceptability and utility of retinoids for treating disease.

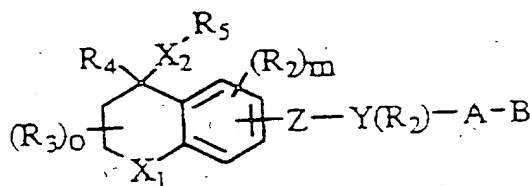
3 It is now general knowledge in the art that two main types of  
4 retinoid receptors exist in mammals (and other organisms). The two  
5 main types or families of receptors respectively designated the RARs  
6 and RXRs. Within each type there are subtypes; in the RAR family the  
7 subtypes are designated RAR $\alpha$ , RAR $\beta$  and RAR $\gamma$ , in RXR the subtypes  
8 are: RXR $\alpha$ , RXB $\beta$  and RXR $\gamma$ . It has also been established in the art  
9 that the distribution of the two main retinoid receptor types, and of the  
10 several sub-types is not uniform in the various tissues and organs of  
11 mammalian organisms. Moreover, it is generally accepted in the art  
12 that many unwanted side effects of retinoids are mediated by one or  
13 more of the RAR receptor subtypes. Accordingly, among compounds  
14 having agonist-like activity at retinoid receptors, specificity or selectivity  
15 for one of the main types or families, and even specificity or selectivity  
16 for one or more subtypes within a family of receptors, is considered a  
17 desirable pharmacological property. Some compounds bind to one or  
18 more RAR receptor subtypes, but do not trigger the response which is  
19 triggered by agonists of the same receptors. A compound that binds to  
20 a biological receptor but does not trigger an agonist-like response is  
21 usually termed an antagonist. Accordingly, the "effect" of compounds  
22 on retinoid receptors may fall in the range of having no effect at all,  
23 (inactive compound, neither agonist nor antagonist), the compound may  
24 elicit an agonist-like response on all receptor subtypes (pan-agonist), or  
25 a compound may be a partial agonist and/or partial antagonist of  
26 certain receptor subtypes if the compound binds to but does not  
27 activate certain receptor subtype or subtypes but elicits an agonist-like  
28 response in other receptor subtype or subtypes. A pan antagonist is a  
29 compound that binds to all known retinoid receptors but does not elicit  
30 an agonist-like response in any of the receptors.

31 It has been recently discovered and described in a pending

1 application assigned to the same assignee as the present application that  
 2 retinoid antagonist-like activity of a compound is also a useful property,  
 3 in that such antagonist compounds can be utilized to block certain  
 4 undesired side effects of retinoids, to serve as antidotes to retinoid  
 5 overdose or poisoning, and may lend themselves to other  
 6 pharmaceutical applications as well. More particularly, regarding the  
 7 published scientific and patent literature in this field, published PCT  
 8 application WO 94/14777 describes certain heterocyclic carboxylic acid  
 9 derivatives which bind to RAR retinoid receptors and are said in the  
 10 application to be useful for treatment of certain diseases or conditions,  
 11 such as acne, psoriasis, rheumatoid arthritis and viral infections. A  
 12 similar disclosure is made in the article by Yoshimura et al. J Med.  
 13 Chem. 1995, 38, 3163-3173. Kaneko et al. Med. Chem Res. (1991)  
 14 1:220-225; Apfel et al. Proc. Natl. Acad. Sci. USA Vol 89 pp 7129-7133  
 15 Augusty 1992 Cell Biology; Eckhardt et al. Toxicology Letters, 70 (1994)  
 16 299-308; Keidel et al. Molecular and Cellular Biology, Vol 14, No. 1,  
 17 Jan. 1994, p 287-298; and Eyrolles et al. J. Med. Chem. 1994, 37,  
 18 1508-1517 describe compounds which have antagonist like activity at one  
 19 or more of the RAR retinoid subtypes.

## 20 SUMMARY OF THE INVENTION

21 The present invention covers compounds of Formula 1



30 Formula 1

31 wherein X<sub>1</sub> is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> where R<sub>1</sub> is independently H or alkyl of 1  
 to 6 carbons, and n is an integer between 0 and 2;

1  $X_2$  is S or O;

2 Z is  $-N=N-$ ,

3  $-N(O)=N-$ ,

4  $-N=N(O)-$ ,

5  $-N=CR_1-$ ,

6  $-CR_1=N$ ,

7  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

8  $-CO-NR_1-$ ,

9  $-CS-NR_1-$ ,

10  $-NR_1-CO$ ,

11  $-NR_1-CS$ ,

12  $-COO-$ ,

13  $-OCO-$ ;

14  $-CSO-$ ;

15  $-OCS-$ ;

16  $-CO-CR_1=CR_1-$ ;

17  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ ,

18 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6

19 carbons, or alkylthio of 1 to 6 carbons;

20  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

21  $m$  is an integer having the value of 0 - 3;

22  $o$  is an integer having the value of 0 - 4;

23  $R_4$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10

24 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons

25 and 1 to 3 triple bonds, carbocyclic aryl selected from the group

26 consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkyl-

27 naphthyl, phenyl- $C_1 - C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl; CN, or

28  $(CH_2)_pCO_2R_8$  where  $p$  is an integer between 0 to 10;

29  $R_5$  is hydrogen, alkyl of 1 to 10 carbons, fluoro-substituted alkyl of

30 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double

31 bonds, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbo-

1 cyclic aryl selected from the group consisting of phenyl,  $C_1$  -  
 2  $C_{10}$ -alkylphenyl, naphthyl,  $C_1$  -  $C_{10}$ -alkylnaphthyl, phenyl- $C_1$  -  $C_{10}$ alkyl,  
 3 naphthyl- $C_1$  -  $C_{10}$ alkyl;  $Si(C_{1-6}alkyl)_3$ ,  $COR_{14}$ , camphanoyl,  
 4  $C(R_{15})(R_{16})X_2R_{17}$ ;

5 Y is a phenyl or naphthyl group, or heteroaryl selected from a  
 6 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 7 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl; said phenyl and  
 8 heteroaryl groups being optionally substituted with one or two  $R_2$   
 9 groups, or

10 when Z is  $-(CR_1=CR_1)_{n'}$  and  $n'$  is 3, 4 or 5 then Y represents a  
 11 direct valence bond between said  $(CR_2=CR_2)_{n'}$  group and B;

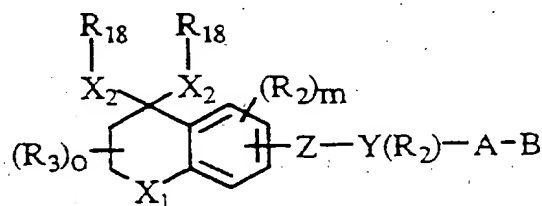
12 A is  $(CH_2)_q$  where q is 0-5, lower branched chain alkyl  
 13 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
 14 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
 15 triple bonds;

16 B is hydrogen, COOH or a pharmaceutically acceptable salt  
 17 thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  $CHO$ ,  
 18  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
 19 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 20 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 21 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 22 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
 23 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 24 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 25 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 26 divalent alkyl radical of 2-5 carbons;

27  $R_{14}$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10  
 28 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons  
 29 and 1 to 3 triple bonds, carbocyclic aryl selected from the group  
 30 consisting of phenyl,  $C_1$  -  $C_{10}$ -alkylphenyl, naphthyl,  $C_1$  -  
 31  $C_{10}$ -alkylnaphthyl, phenyl- $C_1$  -  $C_{10}$ alkyl, naphthyl- $C_1$  -  $C_{10}$ alkyl, and

$R_{15}$  and  $R_{16}$  are hydrogen or lower alkyl of 1 to 6 carbons,  $R_{17}$  is lower alkyl of 1 to 6 carbons, or  $R_{16}$  and  $R_{17}$  jointly form a ring having a total of 4 to 5 carbons and the  $X_2$  heteroatom;

compounds of Formula 2



### Formula 2

wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to 6 carbons, and  $n$  is an integer between 0 and 2;

$X_2$  is S or O;

$Z$  is  $-N=N-$ ,

$-N(O)=N-$ ,

$-N=N(O)-$ ,

$-N=CR_1-$ ,

$-CR_1=N-$ ,

$-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

$-CO-NR_1-$ ,

$-CS-NR_1-$ ,

$-NR_1-CO-$ ,

$-NR_1-CS-$ ,

$-COO-$ ,

$-OCO-$ ;

$-CSO-$ ;

$-OCS-$ ;

$-CO-CR_1=CR_1-$ ;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ ,

1 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
2 carbons, or alkylthio of 1 to 6 carbons;

3  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

4  $m$  is an integer having the value of 0 - 3;

5  $o$  is an integer having the value of 0 - 4;

6  $Y$  is a phenyl or naphthyl group, or heteroaryl selected from a  
7 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
8 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
9 heteroaryl groups being optionally substituted with one or two  $R_2$   
10 groups, or

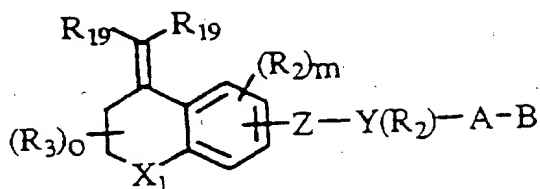
11 when  $Z$  is  $-(CR_1=CR_1)_{n'}$  and  $n'$  is 3, 4 or 5 then  $Y$  represents a  
12 direct valence bond between said  $(CR_2=CR_2)_n$  group and B;

13  $A$  is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl  
14 having 3-6 carbons, cycloalkyl having 3-6 carbons; alkenyl having 2-6  
15 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
16 triple bonds;

17  $B$  is hydrogen, COOH or a pharmaceutically acceptable salt  
18 thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  $CHO$ ,  
19  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
20 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
21 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
22 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
23 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
24 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
25 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
26 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
27 divalent alkyl radical of 2-5 carbons, and

28  $R_{18}$  is alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10  
29 carbons, or the two  $R_{18}$  groups jointly form a ring having a total of 3 to  
30 6 carbons, or the two  $X_1R_{18}$  groups jointly symbolize an oxo ( $=O$ ) or a  
31 thio ( $=S$ ) function, or each of the two  $X_2R_{18}$  groups is H;

compounds of Formula 3



### Formula 3

wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to 6 carbons, and  $n$  is an integer between 0 and 2;

Z is

- N=N-,
- N(O)=N-,
- N=N(O)-,
- N=CR<sub>1</sub>-,
- CR<sub>1</sub>=N,
- (CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- where n' is an integer having the value 0 - 5,
- CO-NR<sub>1</sub>-,
- CS-NR<sub>1</sub>-,
- NR<sub>1</sub>-CO,
- NR<sub>1</sub>-CS,
- COO-,
- OCO-;
- CSO-;
- OCS-;
- CO-CR<sub>1</sub>=CR<sub>1</sub>-;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ , fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons;

R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

o is an integer having the value of 0 - 4;



1 Y is a phenyl or naphthyl group, or heteroaryl selected from a  
 2 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 3 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
 4 heteroaryl groups being optionally substituted with one or two  $R_2$   
 5 groups, or

6 when Z is  $-(CR_1=CR_1)_n-$  and  $n'$  is 3, 4 or 5 then Y represents a  
 7 direct valence bond between said  $(CR_2=CR_2)_n$  group and B;

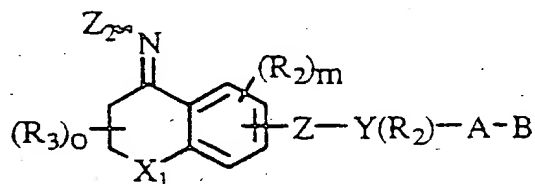
8 A is  $(CH_2)_q$  where q is 0-5, lower branched chain alkyl  
 9 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
 10 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
 11 triple bonds;

12 B is hydrogen, COOH or a pharmaceutically acceptable salt  
 13 thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  $CHO$ ,  
 14  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
 15 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 16 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 17 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 18 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
 19 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 20 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 21 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 22 divalent alkyl radical of 2-5 carbons, and

23  $R_{19}$  is independently hydrogen, alkyl of 1 to 10 carbons,  
 24 fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons  
 25 and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to  
 26 3 triple-bonds, carbocyclic aryl selected from the group consisting of  
 27 phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 -$   
 28  $C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl; heteroaryl selected from the group  
 29 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 30 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 31 groups being optionally substituted with one or two  $R_2$  groups, further

1  $R_{19}$  is independently CN, CHO,  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $(CH_2)_pCO_2R_8$ ,  
 2  $(CH_2)_pCH_2OH$ ,  $(CH_2)_pCH_2OR_{11}$ ,  $(CH_2)_pCH_2OCOR_{11}$ , where p is an  
 3 integer between 0 to 10, or the two  $R_{19}$  groups jointly represent 3 to 8  
 4 methylene groups which together with the alkylidene carbon complete a  
 5 ring, the ring optionally containing 1 to 2 double bonds and the ring  
 6 being optionally substituted with 1 or 2  $R_2$  groups;

7 compounds of Formula 4



15 Formula 4

16 wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1  
 17 to 6 carbons, and n is an integer between 0 and 2;

18 Z is -N=N-,  
 19 -N(O)=N-,  
 20 -N=N(O)-,  
 21 -N=CR<sub>1</sub>-,  
 22 -CR<sub>1</sub>=N-,  
 23 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- where n' is an integer having the value 0 - 5,  
 24 -CO-NR<sub>1</sub>-,  
 25 -CS-NR<sub>1</sub>-,  
 26 -NR<sub>1</sub>-CO,  
 27 -NR<sub>1</sub>-CS,  
 28 -COO-,  
 29 -OCO-,  
 30 -CSO-,  
 31 -OCS-;

1  $-\text{CO}-\text{CR}_1=\text{CR}_1-$ ;

2  $\text{R}_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $\text{CF}_3$ ,  
3 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
4 carbons, or alkylthio of 1 to 6 carbons;

5  $\text{R}_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

6  $m$  is an integer having the value of 0 - 3;

7  $o$  is an integer having the value of 0 - 4;

8  $\text{Y}$  is a phenyl or naphthyl group, or heteroaryl selected from a  
9 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
10 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
11 heteroaryl groups being optionally substituted with one or two  $\text{R}_2$   
12 groups, or

13 when  $\text{Z}$  is  $-(\text{CR}_1=\text{CR}_1)_{n'}$  and  $n'$  is 3, 4 or 5 then  $\text{Y}$  represents a  
14 direct valence bond between said  $(\text{CR}_2=\text{CR}_2)_n$  group and  $\text{B}$ ;

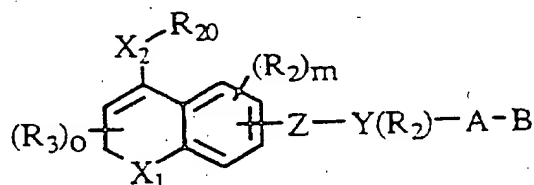
15  $\text{A}$  is  $(\text{CH}_2)_q$  where  $q$  is 0-5, lower branched chain alkyl  
16 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
17 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
18 triple bonds;

19  $\text{B}$  is hydrogen, COOH or a pharmaceutically acceptable salt  
20 thereof,  $\text{COOR}_8$ ,  $\text{CONR}_9\text{R}_{10}$ ,  $-\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{OR}_{11}$ ,  $\text{CH}_2\text{OCOR}_{11}$ , CHO,  
21  $\text{CH}(\text{OR}_{12})_2$ ,  $\text{CHOR}_{13}\text{O}$ ,  $-\text{COR}_7$ ,  $\text{CR}_7(\text{OR}_{12})_2$ ,  $\text{CR}_7\text{OR}_{13}\text{O}$ , or  $\text{Si}(\text{C}_{1-6}\text{alkyl})_3$ ,  
22 where  $\text{R}_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
23 carbons,  $\text{R}_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
24 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
25 10 carbons, or  $\text{R}_8$  is phenyl or lower alkylphenyl,  $\text{R}_9$  and  $\text{R}_{10}$   
26 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
27 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $\text{R}_{11}$  is  
28 lower alkyl, phenyl or lower alkylphenyl,  $\text{R}_{12}$  is lower alkyl, and  $\text{R}_{13}$  is  
29 divalent alkyl radical of 2-5 carbons, and

30  $\text{Z}_2$  is  $\text{OR}_1$  or  $\text{OR}_{18}$  where  $\text{R}_{18}$  is phenyl, benzyl, lower alkyl or  
31 lower alkoxy substituted phenyl, or  $\text{Z}_2$  is  $\text{OSi}(\text{R}_2)_3$ ,  $\text{OCOR}_{14}$ ,

1 OC(R<sub>15</sub>)(R<sub>16</sub>)X<sub>2</sub>R<sub>17</sub>, N(R<sub>14</sub>)<sub>2</sub>, NHCON(R<sub>14</sub>)<sub>2</sub>, NHCSN(R<sub>14</sub>)<sub>2</sub>, where X<sub>2</sub> is  
 2 O or S; R<sub>14</sub> is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10  
 3 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons  
 4 and 1 to 3 triple bonds, carbocyclic aryl selected from the group  
 5 consisting of phenyl, C<sub>1</sub> - C<sub>10</sub>-alkylphenyl, naphthyl, C<sub>1</sub> -  
 6 C<sub>10</sub>-alkylnaphthyl, phenyl-C<sub>1</sub> - C<sub>10</sub>alkyl, naphthyl-C<sub>1</sub> - C<sub>10</sub>alkyl; R<sub>15</sub> and  
 7 R<sub>16</sub> are hydrogen or lower alkyl of 1 to 6 carbons, R<sub>17</sub> is lower alkyl of 1  
 8 to 6 carbons, or R<sub>16</sub> and R<sub>17</sub> jointly form a ring having a total of 4 to 5  
 9 carbons and the X<sub>2</sub> heteroatom;

10 compounds of Formula 5



18 Formula 5

19 wherein X<sub>1</sub> is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> where R<sub>1</sub> is independently H or alkyl of 1  
 20 to 6 carbons, and n is an integer between 0 and 2;

21 Z is -N=N-,

22 -N(O)=N-,

23 -N=N(O)-,

24 -N=CR<sub>1</sub>-,

25 -CR<sub>1</sub>=N,

26 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- where n' is an integer having the value 0 - 5,

27 -CO-NR<sub>1</sub>-,

28 -CS-NR<sub>1</sub>-,

29 -NR<sub>1</sub>-CO,

30 -NR<sub>1</sub>-CS,

31 -COO-,

1 -OCO-;

2 -CSO-;

3 -OCS-;

4 -CO-CR<sub>1</sub>=CR<sub>1</sub>-;

5 R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
6 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
7 carbons, or alkylthio of 1 to 6 carbons;

8 R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;

9 m is an integer having the value of 0 - 3;

10 o is an integer having the value of 0 - 3;

11 Y is a phenyl or naphthyl group, or heteroaryl selected from a  
12 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
13 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and  
14 heteroaryl groups being optionally substituted with one or two R<sub>2</sub>  
15 groups, or

16 when Z is -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- and n' is 3, 4 or 5 then Y represents a  
17 direct valence bond between said (CR<sub>2</sub>=CR<sub>2</sub>)<sub>n</sub> group and B;

18 A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl  
19 having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
20 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
21 triple bonds;

22 B is hydrogen, COOH or a pharmaceutically acceptable salt  
23 thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
24 CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or Si(C<sub>1-6</sub>alkyl)<sub>3</sub>,  
25 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
26 carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
27 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
28 10 carbons, or R<sub>8</sub> is phenyl or lower alkylphenyl, R<sub>9</sub> and R<sub>10</sub>  
29 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
30 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R<sub>11</sub> is  
31 lower alkyl, phenyl or lower alkylphenyl, R<sub>12</sub> is lower alkyl, and R<sub>13</sub> is

divalent alkyl radical of 2-5 carbons;

$X_2$  is O, S, SO or  $SO_2$ , and

$R_{20}$  is  $Si(C_{1-6}alkyl)_3$ ,  $R_{14}$ ,  $COR_{14}$ ,  $SO_2R_{21}$ , where  $R_{14}$  is hydrogen,

alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3

double bond, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds,

carbocyclic aryl selected from the group consisting of phenyl,  $C_1 -$

$C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 - C_{10}$ alkyl,

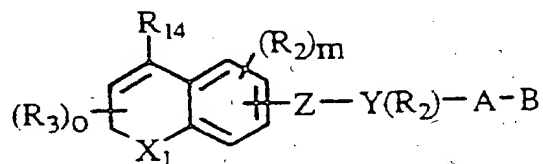
naphthyl- $C_1 - C_{10}$ alkyl, or  $R_{20}$  is hydroxyalkyl, aminoalkyl or thioalkyl

having 1 to 10 carbons; and  $R_{21}$  is alkyl of 1 to 10 carbons, fluoroalkyl of

1 to 10 carbons, or carbocyclic aryl selected from the group consisting of

phenyl,  $C_1 - C_{10}$ -alkylphenyl and phenyl- $C_1 - C_{10}$ alkyl, and

compounds of Formula 6



Formula 6

wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to 6 carbons, and  $n$  is an integer between 0 and 2;

$Z$  is  $-N=N-$ ,

$-N(O)=N-$ ,

$-N=N(O)-$ ,

$-N=CR_1-$ ,

$-CR_1=N$ ,

$-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

$-CO-NR_1-$ ,

$-CS-NR_1-$ ,

$-NR_1-CO$ ,

1                   -NR<sub>1</sub>-CS,  
 2                   -COO-,  
 3                   -OCO-;  
 4                   -CSO-;  
 5                   -OCS-;  
 6                   -CO-CR<sub>1</sub>=CR<sub>1</sub>-;

7           R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
 8   fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
 9   carbons, or alkylthio of 1 to 6 carbons;

10          R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;

11          m is an integer having the value of 0 - 3;

12          o is an integer having the value of 0 - 3;

13          Y is a phenyl or naphthyl group, or heteroaryl selected from a  
 14   group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 15   pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and  
 16   heteroaryl groups being optionally substituted with one or two R<sub>2</sub>  
 17   groups, or

18          when Z is -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- and n' is 3, 4 or 5 then Y represents a  
 19   direct valence bond between said (CR<sub>2</sub>=CR<sub>2</sub>)<sub>n</sub> group and B;

20          A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl  
 21   having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6  
 22   carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2  
 23   triple bonds;

24          B is hydrogen, COOH or a pharmaceutically acceptable salt  
 25   thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
 26   CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or Si(C<sub>1-6</sub>alkyl)<sub>3</sub>,  
 27   where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 28   carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 29   where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 30   10 carbons, or R<sub>8</sub> is phenyl or lower alkylphenyl, R<sub>9</sub> and R<sub>10</sub>  
 31   independently are hydrogen, an alkyl group of 1 to 10 carbons, or a

1 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 2 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 3 divalent alkyl radical of 2-5 carbons; and

4  $R_{14}$  is  $(R_{15})_r$ -substituted alkyl of 1 - 6 carbons,  $(R_{15})_r$ -substituted  
 5 alkenyl of 1 - 6 carbons and 1 or 2 double bonds,  $(R_{15})_r$ -substituted  
 6 alkynyl of 1 - 6 carbons and 1 or 2 triple bonds,  $(R_{15})_r$ -phenyl,  
 7  $(R_{15})_r$ -naphthyl, or  $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to  
 8 3 heteroatoms selected from the group consisting of O, S and N, r is an  
 9 integer having the values of 0 - 5, and

10  $R_{15}$  is independently H, F, Cl, Br, I,  $NO_2$ ,  $N(R_8)_2$ ,  $N(R_8)COR_8$ ,  
 11  $NR_8CON(R_8)_2$ , OH,  $OCOR_8$ ,  $OR_8$ , CN,  $COOH$ ,  $COOR_8$  an alkyl group  
 12 having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10  
 13 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double  
 14 bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or  
 15 a (trialkyl)silyl or (trialkyl)silyloxy group where the alkyl groups  
 16 independently have 1 to 6 carbons.

17 In a second aspect, this invention relates to the use of the  
 18 compounds of **Formula 1** through **Formula 6** for the treatment of  
 19 skin-related diseases, including, without limitation, actinic keratoses,  
 20 arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis,  
 21 ichthyoses and other keratinization and hyperproliferative disorders of  
 22 the skin, eczema, atopic dermatitis, Darriers disease, lichen planus,  
 23 prevention and reversal of glucocorticoid damage (steroid atrophy), as a  
 24 topical anti-microbial, as skin anti-pigmentation agents and to treat and  
 25 reverse the effects of age and photo damage to the skin. The  
 26 compounds are also useful for the prevention and treatment of  
 27 cancerous and precancerous conditions, including, premalignant and  
 28 malignant hyperproliferative diseases such as cancers of the breast, skin,  
 29 prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx,  
 30 oral cavity, blood and lymphatic system, metaplasias, dysplasias,  
 31 neoplasias, leukoplakias and papillomas of the mucous membranes and



1 in the treatment of Kaposi's sarcoma. In addition, the present  
2 compounds can be used as agents to treat diseases of the eye, including,  
3 without limitation, proliferative vitreoretinopathy (PVR), retinal  
4 detachment, dry eye and other corneopathies, as well as in the  
5 treatment and prevention of various cardiovascular diseases, including,  
6 without limitation, diseases associated with lipid metabolism such as  
7 dyslipidemias, prevention of post-angioplasty restenosis and as an agent  
8 to increase the level of circulating tissue plasminogen activator (TPA).  
9 Other uses for the compounds of the present invention include the  
10 prevention and treatment of conditions and diseases associated with  
11 Human papilloma virus (HPV), including warts and genital warts,  
12 various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis  
13 and Krohn's disease, neurodegenerative diseases such as Alzheimer's  
14 disease, Parkinson's disease and stroke, improper pituitary function,  
15 including insufficient production of growth hormone, modulation of  
16 apoptosis, including both the induction of apoptosis and inhibition of  
17 T-Cell activated apoptosis, restoration of hair growth, including  
18 combination therapies with the present compounds and other agents  
19 such as Minoxidil<sup>R</sup>, diseases associated with the immune system,  
20 including use of the present compounds as immunosuppressants and  
21 immunostimulants, modulation of organ transplant rejection and  
22 facilitation of wound healing, including modulation of chelosis.

23 Alternatively, those compounds of the invention which act as  
24 antagonists of one or more retinoid receptor subtypes are useful to  
25 prevent certain undesired side effects of retinoids which are  
26 administered for the treatment or prevention of certain diseases or  
27 conditions. For this purpose the retinoid antagonist compounds of the  
28 invention may be co-administered with retinoids. The compounds of  
29 the present invention are also useful in the treatment of acute or  
30 chronic toxicity resulting from overdose or poisoning by retinoid drugs  
31 or Vitamin A.

1 This invention also relates to a pharmaceutical formulation  
2 comprising a compound of Formula 1 through Formula 6 in admixture  
3 with a pharmaceutically acceptable excipient, said formulation being  
4 adapted for administration to a mammal, including a human being, to  
5 treat or alleviate the conditions which were described above as treatable  
6 by retinoids, to be co-administered with retinoids to eliminate or  
7 reduce side effects of retinoids, or to treat retinoid or Vitamin A  
8 overdose or poisoning.

### 9 BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

#### 10 Assay of Retinoid-like or Retinoid Antagonist-like Biological Activity

11 A classic measure of retinoic acid activity involves measuring the  
12 effects of retinoic acid on ornithine decarboxylase. The original work  
13 on the correlation between retinoic acid and decrease in cell  
14 proliferation was done by Verma & Boutwell, Cancer Research, 1977,  
15 37,2196-2201. That reference discloses that ornithine decarboxylase  
16 (ODC) activity increased precedent to polyamine biosynthesis. It has  
17 been established elsewhere that increases in polyamine synthesis can be  
18 correlated or associated with cellular proliferation. Thus, if ODC  
19 activity could be inhibited, cell hyperproliferation could be modulated.  
20 Although all cases for ODC activity increases are unknown, it is known  
21 that 12-O-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity.  
22 Retinoic acid inhibits this induction of ODC activity by TPA. An assay  
23 essentially following the procedure set out in Cancer Research:  
24 1662-1670, 1975 may be used to demonstrate inhibition of TPA induction  
25 of ODC by compounds of this invention. Activity of exemplary  
26 compounds of the present invention in the above-described ODC assay  
27 is disclosed in Table 1 which provides the  $IC_{60}$  concentration for the  
28 respective exemplary compound. (" $IC_{60}$ " is that concentration of the test  
29 compound which causes 60% inhibition in the ODC assay. By analogy,  
30 " $IC_{50}$ , for example, is that concentration of the test compound which  
31 causes 50% inhibition in the ODC assay.)

TABLE 1  
ODC Assay

| Compound No. | IC <sub>50</sub> (nmols) |
|--------------|--------------------------|
| A5           | 10.3                     |
| D3           | 8.4                      |
| C22b         | 10                       |
| E24          | 8.3                      |
| A16          | 4.3 (IC <sub>80</sub> )  |
| C14          | 4                        |
| E79          | 5.3                      |
| D34          | 4.3 (IC <sub>80</sub> )  |
| C15          | 14.5                     |
| E15          | 24.7                     |
| A27          | 0.7                      |
| E16          | 88.4                     |
| A23          | 43.7                     |
| A2           | 27                       |
| E72b         | 18                       |
| E56a         | 3.1                      |
| D6           | 1.9                      |

Other assays described below, measure the ability of the compounds of the present invention to bind to, and/or activate various retinoid receptor subtypes. When in these assays a compound binds to a given receptor subtype and activates the transcription of a reporter gene through that subtype, then the compound is considered an **agonist** of that receptor subtype. Conversely, a compound is considered an **antagonist** of a given receptor subtype if in the below described co-transfection assays the compound does not cause significant transcriptional activation of the receptor regulated reporter gene, but nevertheless binds to the receptor with a K<sub>d</sub> value of less than approximately 1 micromolar. In the below described assays the ability of the compounds to bind to RAR<sub>α</sub>, RAR<sub>β</sub>, RAR<sub>γ</sub>, RXR<sub>α</sub>, RXR<sub>β</sub> and RXR<sub>γ</sub> receptors, and the ability or inability of the compounds to activate transcription of a reporter gene through these receptor subtypes

1 can be tested.

2 Specifically, a chimeric receptor transactivation assay which tests  
3 for agonist-like activity in the RAR $\alpha$ , RAR $\beta$ , RAR $\gamma$ , RXR $\alpha$  receptor  
4 subtypes, and which is based on work published by Feigner P. L. and  
5 Holm M. (1989) Focus, 11 2 is described in detail in United States  
6 Patent No. 5,455,265 the specification of which is hereby expressly  
7 incorporated by reference.

8 A holoreceptor transactivation assay and a ligand binding assay  
9 which measure the antagonist/agonist like activity of the compounds of  
10 the invention, or their ability to bind to the several retinoid receptor  
11 subtypes, respectively, are described in published PCT Application No.  
12 WO WO93/11755 (particularly on pages 30 - 33 and 37 - 41) published  
13 on June 24, 1993, the specification of which is also incorporated herein  
14 by reference. A description of the holoreceptor transactivation assay is  
15 also provided below.

#### 16 HOLORECEPTOR TRANSACTIVATION ASSAY

17 CV1 cells (5,000 cells/well) were transfected with an RAR  
18 reporter plasmid MTV-TREp-LUC (50 ng) along with one of the RAR  
19 expression vectors (10 ng) in an automated 96-well format by the  
20 calcium phosphate procedure of Hevman et al. Cell 68, 397 - 406,  
21 (1992). For RXR $\alpha$  and RXR $\gamma$  transactivation assays, an RXR-responsive  
22 reporter plasmid CRBP-II-tk-LUC (50 ng) along with the appropriate  
23 RXR expression vectors (10 ng) was used substantially as described by  
24 Hevman et al. above, and Allegretto et al. J. Biol. Chem. 268, 26625 -  
25 26633. For RXR $\beta$  transactivation assays, an RXR-responsive reporter  
26 plasmid CPRE-tk-LUC (50 ng) along with RXR $\beta$  expression vector (10  
27 ng) was used as described in above. These reporters contain DRI  
28 elements from human CRBP-II and certain DRI elements from  
29 promoter, respectively. (see Mangelsdorf et al. The Retinoids: Biology,  
30 Chemistry and Medicine, pp 319 - 349, Raven Press Ltd., New York and  
31 Heyman et al., cited above) (1, 8). A  $\beta$ -galactosidase (50 ng) expression

1 vector was used as an internal control in the transfections to normalize  
2 for variations in transfection efficiency. The cells were transfected in  
3 triplicate for 6 hours, followed by incubation with retinoids for 36 hours,  
4 and the extracts were assayed for luciferase and  $\beta$ -galactosidase  
5 activities. The detailed experimental procedure for holoreceptor  
6 transactivations has been described in Heyman et al. above, and  
7 Allegretto et al. cited above. The results obtained in this assay are  
8 expressed in  $EC_{50}$  numbers, as they are also in the chimeric receptor  
9 transactivation assay. The Heyman et al. Cell 68, 397 - 406, Allegretto  
10 et al. J. Biol. Chem. 268, 26625 - 26633, and Mangelsdorf et al. The  
11 Retinoids: Biology, Chemistry and Medicine, pp 319 - 349, Raven Press  
12 Ltd., New York, are expressly incorporated herein by reference. The  
13 results of ligand binding assay are expressed in  $K_d$  numbers. (See  
14 Cheng et al. Biochemical Pharmacology Vol. 22 pp 3099-3108, expressly  
15 incorporated herein by reference.)

16 Table 2 shows the results of the ligand binding assay for certain  
17 exemplary compounds of the invention for the receptor subtypes in the  
18 RAR group.

**TABLE 2**  
**Ligand Binding Assay**

| Compound<br>No. | K <sub>d</sub> (nanomolar, nM) |             |              |
|-----------------|--------------------------------|-------------|--------------|
|                 | RAR $\alpha$                   | RAR $\beta$ | RAR $\gamma$ |
| A6              | 125                            | 36          | 127          |
| D4              | 1000                           | 132         | 363          |
| C25             | 19                             | 12          | 42           |
| E27             | 551                            | 535         | >1000        |
| A18             | 538                            | 193         | 162          |
| E80             | 394                            | 531         | 901          |
| D34             | 235                            | 200         | 530          |
| E14             | 36                             | 35          | 455          |
| A28             | 4                              | 3           | 42           |
| E17             | 192                            | 378         | >1000        |
| A24             | 283                            | 92          | 259          |
| A2a             | 150                            | 219         | 421          |
| E67             | 77                             | 302         | 375          |
| D7              | >1000                          | 226         | >1000        |

#### Modes of Administration

The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations.

In the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne or psoriasis, oral administration may also be used. Any common topical formulation such as a solution, suspension, gel, ointment, or salve and the like may be used. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, by Remington's Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania. For topical application, these compounds could also be administered as a powder or spray, particularly in aerosol form. If the

1 drug is to be administered systemically, it may be confected as a  
2 powder, pill, tablet or the like or as a syrup or elixir suitable for oral  
3 administration. For intravenous or intraperitoneal administration, the  
4 compound will be prepared as a solution or suspension capable of being  
5 administered by injection. In certain cases, it may be useful to  
6 formulate these compounds by injection. In certain cases, it may be  
7 useful to formulate these compounds in suppository form or as extended  
8 release formulation for deposit under the skin or intramuscular  
9 injection.

10 Other medicaments can be added to such topical formulation for  
11 such secondary purposes as treating skin dryness; providing protection  
12 against light; other medications for treating dermatoses; medicaments  
13 for preventing infection, reducing irritation, inflammation and the like.

14 Treatment of dermatoses or any other indications known or  
15 discovered to be susceptible to treatment by retinoic acid-like  
16 compounds will be effected by administration of the therapeutically  
17 effective dose of one or more compounds of the instant invention. A  
18 therapeutic concentration will be that concentration which effects  
19 reduction of the particular condition, or retards its expansion. In certain  
20 instances, the compound potentially may be used in prophylactic  
21 manner to prevent onset of a particular condition.

22 A useful therapeutic or prophylactic concentration will vary from  
23 condition to condition and in certain instances may vary with the  
24 severity of the condition being treated and the patient's susceptibility to  
25 treatment. Accordingly, no single concentration will be uniformly  
26 useful, but will require modification depending on the particularities of  
27 the disease being treated. Such concentrations can be arrived at  
28 through routine experimentation. However, it is anticipated that in the  
29 treatment of, for example, acne, or similar dermatoses, that a  
30 formulation containing between 0.01 and 1.0 milligrams per milliliter of  
31 formulation will constitute a therapeutically effective concentration for

1 total application. If administered systemically, an amount between 0.01  
2 and 5 mg per kg per day of body weight would be expected to effect a  
3 therapeutic result in the treatment of many diseases for which these  
4 compounds are useful.

5 Those partial or pan retinoid antagonist compounds of the  
6 invention, when used to take advantage of their antagonist property, can  
7 be co-administered to mammals, including humans, with retinoid  
8 agonists and, by means of pharmacological selectivity or site-specific  
9 delivery, preferentially prevent the undesired effects of certain retinoid  
10 agonists. The antagonist compounds of the invention can also be used  
11 to treat Vitamin A overdose, acute or chronic, resulting either from the  
12 excessive intake of vitamin A supplements or from the ingestion of liver  
13 of certain fish and animals that contain high levels of Vitamin A. Still  
14 further, the antagonist compounds of the invention can also be used to  
15 treat acute or chronic toxicity caused by retinoid drugs. It has been  
16 known in the art that the toxicities observed with hypervitaminosis A  
17 syndrome (headache, skin peeling, bone toxicity, dyslipidemias) are  
18 similar or identical with toxicities observed with other retinoids,  
19 suggesting a common biological cause, that is RAR activation. Because  
20 the antagonist compounds of the present invention block RAR  
21 activation, they are suitable for treating the foregoing toxicities.

22 Generally speaking, for therapeutic applications in mammals, the  
23 antagonist compounds of the invention can be administered enterally or  
24 topically as an antidote to vitamin A, or antidote to retinoid toxicity  
25 resulting from overdose or prolonged exposure, after intake of the  
26 causative factor (vitamin A, vitamin A precursor, or other retinoid) has  
27 been discontinued. Alternatively, the antagonist compounds of the  
28 invention are co-administered with retinoid drugs, in situations where  
29 the retinoid provides a therapeutic benefit, and where the  
30 co-administered antagonist compound alleviates or eliminates one or  
31 more undesired side effects of the retinoid. For this type of application



1 the antagonist compound may be administered in a site-specific manner,  
2 for example as a topically applied cream or lotion while the  
3 co-administered retinoid may be given enterally. For therapeutic  
4 applications the antagonist compounds of the invention, like the retinoid  
5 agonists compounds, are incorporated into pharmaceutical  
6 compositions, such as tablets, pills, capsules, solutions, suspensions,  
7 creams, ointments, gels, salves, lotions and the like, using such  
8 pharmaceutically acceptable excipients and vehicles which per se are  
9 well known in the art. For topical application, the antagonist  
10 compounds of the invention could also be administered as a powder or  
11 spray, particularly in aerosol form. If the drug is to be administered  
12 systemically, it may be confected as a powder, pill, tablet or the like or  
13 as a syrup or elixir suitable for oral administration. For intravenous or  
14 intraperitoneal administration, the compound will be prepared as a  
15 solution or suspension capable of being administered by injection. In  
16 certain cases, it may be useful to formulate these compounds by  
17 injection. In certain cases, it may be useful to formulate these  
18 compounds in suppository form or as extended release formulation for  
19 deposit under the skin or intramuscular injection.

20 The antagonist compounds also, like the retinoid agonists of the  
21 invention, will be administered in a therapeutically effective dose. A  
22 therapeutic concentration will be that concentration which effects  
23 reduction of the particular condition, or retards its expansion. When  
24 co-administering the compounds of the invention to block  
25 retinoid-induced toxicity or side effects, the antagonist compounds of  
26 the invention are used in a prophylactic manner to prevent onset of a  
27 particular condition, such as skin irritation.

28 A useful therapeutic or prophylactic concentration will vary from  
29 condition to condition and in certain instances may vary with the  
30 severity of the condition being treated and the patient's susceptibility to  
31 treatment. Accordingly, no single concentration will be uniformly

1 useful, but will require modification depending on the particularities of  
2 the chronic or acute retinoid toxicity or related condition being treated.  
3 Such concentrations can be arrived at through routine experimentation.  
4 However, it is anticipated that a formulation containing between 0.01  
5 and 1.0 milligrams per milliliter of formulation will constitute a  
6 therapeutically effective concentration for total application. If  
7 administered systemically, an amount between 0.01 and 5 mg per kg per  
8 day of body weight would be expected to effect a therapeutic result.

## 9 **GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY**

### 10 **Definitions**

11 The term alkyl refers to and covers any and all groups which are  
12 known as normal alkyl, branched-chain alkyl and cycloalkyl. The term  
13 alkenyl refers to and covers normal alkenyl, branch chain alkenyl and  
14 cycloalkenyl groups having one or more sites of unsaturation. Similarly,  
15 the term alkynyl refers to and covers normal alkynyl, and branch chain  
16 alkynyl groups having one or more triple bonds.

17 Lower alkyl means the above-defined broad definition of alkyl  
18 groups having 1 to 6 carbons in case of normal lower alkyl, and as  
19 applicable 3 to 6 carbons for lower branch chained and cycloalkyl  
20 groups. Lower alkenyl is defined similarly having 2 to 6 carbons for  
21 normal lower alkenyl groups, and 3 to 6 carbons for branch chained and  
22 cyclo- lower alkenyl groups. Lower alkynyl is also defined similarly,  
23 having 2 to 6 carbons for normal lower alkynyl groups, and 4 to 6  
24 carbons for branch chained lower alkynyl groups.

25 The term "ester" as used here refers to and covers any compound  
26 falling within the definition of that term as classically used in organic  
27 chemistry. It includes organic and inorganic esters. Where **B** (of  
28 **Formula 1** through **6**) is  $\text{-COOH}$ , this term covers the products derived  
29 from treatment of this function with alcohols or thiols preferably with  
30 aliphatic alcohols having 1-6 carbons. Where the ester is derived from  
31 compounds where **B** is  $\text{-CH}_2\text{OH}$ , this term covers compounds derived

1 from organic acids capable of forming esters including phosphorous  
2 based and sulfur based acids, or compounds of the formula  
3  $-\text{CH}_2\text{OCOR}_{11}$  where  $\text{R}_{11}$  is any substituted or unsubstituted aliphatic,  
4 aromatic, heteroaromatic or aliphatic aromatic group, preferably with  
5 1-6 carbons in the aliphatic portions.

6 Unless stated otherwise in this application, preferred esters are  
7 derived from the saturated aliphatic alcohols or acids of ten or fewer  
8 carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and  
9 acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are  
10 those derived from lower alkyl acids and alcohols. Also preferred are  
11 the phenyl or lower alkyl phenyl esters.

12 Amides has the meaning classically accorded that term in organic  
13 chemistry. In this instance it includes the unsubstituted amides and all  
14 aliphatic and aromatic mono- and di- substituted amides. Unless stated  
15 otherwise in this application, preferred amides are the mono- and  
16 di-substituted amides derived from the saturated aliphatic radicals of ten  
17 or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals  
18 of 5 to 10 carbon atoms. Particularly preferred amides are those  
19 derived from substituted and unsubstituted lower alkyl amines. Also  
20 preferred are mono- and disubstituted amides derived from the  
21 substituted and unsubstituted phenyl or lower alkylphenyl amines.  
22 Unsubstituted amides are also preferred.

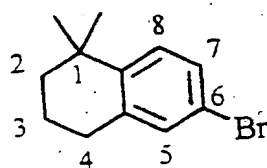
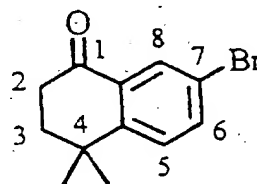
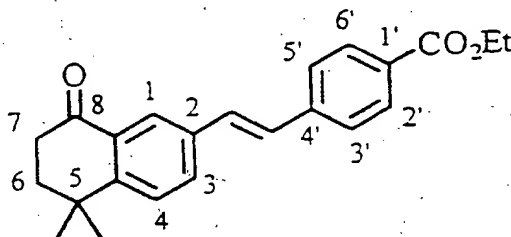
23 Acetals and ketals include the radicals of the formula-CK where  
24 K is  $(-\text{OR})_2$ . Here, R is lower alkyl. Also, K may be  $-\text{OR}_7\text{O}-$  where  $\text{R}_7$   
25 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

26 A pharmaceutically acceptable salt may be prepared for any  
27 compounds in this invention having a functionality capable of forming a  
28 salt, for example an acid functionality. A pharmaceutically acceptable  
29 salt is any salt which retains the activity of the parent compound and  
30 does not impart any deleterious or untoward effect on the subject to  
31 which it is administered and in the context in which it is administered.

1           Pharmaceutically acceptable salts may be derived from organic or  
2 inorganic bases. The salt may be a mono or polyvalent ion. Of  
3 particular interest are the inorganic ions, sodium, potassium, calcium,  
4 and magnesium. Organic salts may be made with amines, particularly  
5 ammonium salts such as mono-, di- and trialkyl amines or ethanol  
6 amines. Salts may also be formed with caffeine, tromethamine and  
7 similar molecules. Where there is a nitrogen sufficiently basic as to be  
8 capable of forming acid addition salts, such may be formed with any  
9 inorganic or organic acids or alkylating agent such as methyl iodide.  
10 Preferred salts are those formed with inorganic acids such as  
11 hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of  
12 simple organic acids such as mono-, di- or tri- acid may also be used.

13           Some of the compounds of the present invention may have *trans*  
14 and *cis* (*E* and *Z*) isomers. In addition, the compounds of the present  
15 invention may contain one or more chiral centers and therefore may  
16 exist in enantiomeric and diastereomeric forms. Still further oxime and  
17 related compounds of the present invention may exist in *syn* and *anti*  
18 isomeric forms. The scope of the present invention is intended to cover  
19 all such isomers *per se*, as well as mixtures of *cis* and *trans* isomers,  
20 mixtures of *syn* and *anti* isomers, mixtures of diastereomers and racemic  
21 mixtures of enantiomers (optical isomers) as well. In the present  
22 application when no specific mention is made of the configuration (*cis*,  
23 *trans*, *syn* or *anti* or *R* or *S*) of a compound (or of an asymmetric  
24 carbon) then a mixture of such isomers, or either one of the isomers is  
25 intended. In a similar vein, when in the chemical structural formulas of  
26 this application a straight line representing a valence bond is drawn to  
27 an asymmetric carbon, then isomers of both *R* and *S* configuration, as  
28 well as their mixtures are intended. Defined stereochemistry about an  
29 asymmetric carbon is indicated in the formulas (where applicable) by a  
30 solid triangle showing  $\beta$  configuration, or by a hashed line showing  $\alpha$   
31 configuration.

1 Referring now to the nomenclature used in naming the  
2 compounds of the invention and intermediate compounds leading  
3 thereto, the system for numbering the tetrahydronaphthalene ring is  
4 demonstrated as shown by the structural formulas of **Compounds F, G**  
5 and **A2**. **Compound A2** is an exemplary compound of the invention  
6 within the scope of **Formula 2** and **Compounds F** and **G** are two  
7 exemplary intermediates utilized in the synthesis of the compounds of  
8 the invention. The numbering systems illustrated here corresponds  
9 substantially to IUPAC rules, and will be readily apparent to those  
10 skilled in the art as it is applied in the ensuing description.

**Compound F****Compound G****Compound A2**

28 Generally speaking, the compounds of the invention are made in  
29 synthetic steps which involve the formation of the  
30 tetrahydronaphthalene, dihydronaphthalene, indane or suberane  
31 moiety, substituted with the desired  $R_1$ ,  $R_2$  and  $R_3$  groups and with a

1 reactive group, such as bromo group, that allows coupling with a reagent  
2 that introduces the  $-Z-Y(R_2)-A-B$  group. Such a reagent can be  
3 generally described as  $X_3-Z-Y(R_2)-A-B$   
4 where  $X_3$  is a reactive group, in many instances a leaving group, such as  
5 halogen. The  $-Z-Y(R_2)-A-B$  group may also be formed in a series of  
6 reactions performed starting with the tetrahydronaphthalene,  
7 dihydronaphthalene, indane or suberane molecule that has the  
8 appropriate reactive group or reactive position. in the aromatic nucleus.

9 The substituent or substituents in the 5 or 8 positions of the  
10 tetrahydronaphthalene or dihydronaphthalene (and by analogy in the  
11 corresponding positions of indane and suberan) which are designated as  
12  $R_4$  and  $X_2R_5$  in Formula 1, as  $(X_2R_{18})_2$  in Formula 2,  $=C(R_{19})_2$  in  
13 Formula 3,  $N=Z_2$  in Formula 4,  $X_2R_{20}$  in Formula 5 and  $R_{14}$  in Formula  
14 6 may be introduced into the tetrahydronaphthalene or  
15 dihydronaphthalene ring moiety before coupling with the reagent  $X_3-Z-$   
16  $Y(R_2)-A-B$ , or before formation of the  $-Z-Y(R_2)-A-B$  group. In other  
17 examples coupling with the reagent  $X_3-Z-Y(R_2)-A-B$  or formation of  
18 the  $-Z-Y(R_2)-A-B$  group attached to the tetrahydronaphthalene or  
19 dihydronaphthalene nucleus is performed first to yield an intermediate  
20 that includes the tetrahydronaphthalene, dihydronaphthalene (and by  
21 analogy indane or suberane) moiety covalently linked to the  $-Z-Y(R_2)-A-$   
22  $B$  group, but which has a reactive group, preferably such as an oxo or  
23 trifluoromethanesulfonyloxy function, in the 5 or 8 position. In these  
24 cases the substituents of these two positions, as defined in Formulas 1 -  
25 6, are introduced into the intermediate by appropriate reactions which  
26 are described in detail below.

27 The synthetic methodology employed for the synthesis of the  
28 compounds of the present invention may also include transformations of  
29 the group designated as  $-A-B$  in Formulas 1 - 6. Generally speaking  
30 these transformations involve reactions well within the skill of the  
31 practicing organic chemist. In this regard the following well known and

1 published general principles and synthetic methodology are briefly  
2 described.

3 Carboxylic acids are typically esterified by refluxing the acid in a  
4 solution of the appropriate alcohol in the presence of an acid catalyst  
5 such as hydrogen chloride or thionyl chloride. Alternatively, the  
6 carboxylic acid can be condensed with the appropriate alcohol in the  
7 presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The  
8 ester is recovered and purified by conventional means. Acetals and  
9 ketals are readily made by the method described in March, "Advanced  
10 Organic Chemistry," 2nd Edition, McGraw-Hill Book Company, p 810).  
11 Alcohols, aldehydes and ketones all may be protected by forming  
12 respectively, ethers and esters, acetals or ketals by known methods such  
13 as those described in McOmie, Plenum Publishing Press, 1973 and  
14 Protecting Groups, Ed. Greene, John Wiley & Sons, 1981.

15 To increase the value of n in the compounds of  $X_3-Z-Y(R_2)-A-B$   
16 or precursors thereof, before affecting the coupling or linkage with the  
17 tetrahydronaphthalene, dihydronaphthalene nucleus (where such  
18 compounds are not available from a commercial source) aromatic or  
19 heteroaromatic carboxylic acids are subjected to homologation by  
20 successive treatment under Arndt-Eistert conditions or other  
21 homologation procedures. Alternatively, derivatives which are not  
22 carboxylic acids may also be homologated by appropriate procedures.  
23 The homologated acids can then be esterified by the general procedure  
24 outlined in the preceding paragraph.

25 Compounds of formula  $X_3-Z-Y(R_2)-A-B$  (or of the invention  
26 as set forth in Formulas 1 through 6, as applicable) where A is an  
27 alkenyl group having one or more double bonds can be made for  
28 example, by synthetic schemes well known to the practicing organic  
29 chemist; for example by Wittig and like reactions, or by introduction of  
30 a double bond by elimination of halogen from an  
31 alpha-halo-arylalkyl-carboxylic acid, ester or like carboxaldehyde.

1 Compounds of formula  $X_3-Z-Y(R_2)-A-B$  (or of the invention as set  
2 forth in **Formulas 1** through **6**, as applicable) where the **A** group has a  
3 triple (acetylenic) bond can be made by reaction of a corresponding  
4 aromatic methyl ketone with strong base, such as lithium diisopropyl  
5 amide, reaction with diethyl chlorophosphate and subsequent addition  
6 of lithium diisopropylamide.

7       The acids and salts derived from compounds of the invention are  
8 readily obtainable from the corresponding esters. Basic saponification  
9 with an alkali metal base will provide the acid. For example, an ester of  
10 the invention may be dissolved in a polar solvent such as an alkanol,  
11 preferably under an inert atmosphere at room temperature, with about  
12 a three molar excess of base, for example, lithium hydroxide or  
13 potassium hydroxide. The solution is stirred for an extended period of  
14 time, between 15 and 20 hours, cooled, acidified and the hydrolysate  
15 recovered by conventional means.

16       The amide may be formed by any appropriate amidation means  
17 known in the art from the corresponding esters or carboxylic acids. One  
18 way to prepare such compounds is to convert an acid to an acid chloride  
19 and then treat that compound with ammonium hydroxide or an  
20 appropriate amine. For example, the ester is treated with an alcoholic  
21 base solution such as ethanolic KOH (in approximately a 10% molar  
22 excess) at room temperature for about 30 minutes. The solvent is  
23 removed and the residue taken up in an organic solvent such as diethyl  
24 ether, treated with a dialkyl formamide and then a 10-fold excess of  
25 oxalyl chloride. This is all effected at a moderately reduced  
26 temperature between about -10 degrees and +10 degrees C. The last  
27 mentioned solution is then stirred at the reduced temperature for 1-4  
28 hours, preferably 2 hours. Solvent removal provides a residue which is  
29 taken up in an inert organic solvent such as benzene, cooled to about 0  
30 degrees C and treated with concentrated ammonium hydroxide. The  
31 resulting mixture is stirred at a reduced temperature for 1 - 4 hours.



1 The product is recovered by conventional means.

2 Alcohols are made by converting the corresponding acids to the  
3 acid chloride with thionyl chloride or other means (J. March, "Advanced  
4 Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then  
5 reducing the acid chloride with sodium borohydride (March, Ibid, pg.  
6 1124), which gives the corresponding alcohols. Alternatively, esters may  
7 be reduced with lithium aluminum hydride at reduced temperatures.  
8 Alkylating these alcohols with appropriate alkyl halides under  
9 Williamson reaction conditions (March, Ibid, pg. 357) gives the  
10 corresponding ethers. These alcohols can be converted to esters by  
11 reacting them with appropriate acids in the presence of acid catalysts or  
12 dicyclohexylcarbodiimide and dimethylaminopyridine.

13 Aldehydes can be prepared from the corresponding primary  
14 alcohols using mild oxidizing agents such as pyridinium dichromate in  
15 methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or  
16 dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K.,  
17 Swern, D., Tetrahedron, 1978, 34, 1651).

18 Ketones can be prepared from an appropriate aldehyde by  
19 treating the aldehyde with an alkyl Grignard reagent or similar reagent  
20 followed by oxidation.

21 Acetals or ketals can be prepared from the corresponding  
22 aldehyde or ketone by the method described in March, Ibid, p 810.

23 Reagents of formula  $X_3-Z-Y(R_2)-A-B$  (or compounds of the  
24 invention as set forth in Formulas 1 through 6, as applicable) where B is  
25 H can be prepared from the corresponding halogenated aromatic or  
26 heteroaromatic compounds, preferably where the halogen is I.

## 27 SPECIFIC EMBODIMENTS

28 With reference to the symbol Y in Formulas 1 through 6, the  
29 preferred compounds of the invention are those where Y is phenyl,  
30 naphthyl, pyridyl, thienyl or furyl. Even more preferred are compounds  
31 where Y is phenyl, naphthyl or pyridyl. As far as substitutions on the

1 Y (phenyl), Y (pyridyl) and (Y) naphthyl groups are concerned,  
 2 compounds are preferred where the phenyl group is 1,4 (para)  
 3 substituted, the naphthyl group is 2,6 substituted and where the pyridine  
 4 ring is 2,5 substituted. (Substitution in the 2,5 positions in the "pyridine"  
 5 nomenclature corresponds to substitution in the 6-position in the  
 6 "nicotinic acid" nomenclature.) In the preferred compounds of the  
 7 invention there is no optional  $R_2$  substituent on the Y group.

8 The A-B group of the preferred compounds is  $(CH_2)_n-COOH$  or  
 9  $(CH_2)_n-COOR_8$ , where  $R_8$  is defined as above. Even more preferably n  
 10 is zero and  $R_8$  is lower alkyl.

11 Referring still to the preferred compounds of **Formulas 1** through  
 12 **6**, the  $X_1$  group is preferably  $C(R_1)_2$ , that is the preferred compounds  
 13 are tetrahydronaphthalene or dihydronaphthalene derivatives. The  
 14 aromatic portion of the tetrahydronaphthalene or dihydronaphthalene  
 15 moiety is preferably substituted only by the  $-Z-Y(R_2)-A-B$  group. In  
 16 other words, in the preferred compounds there is no  $R_2$  substituent  
 17 (other than hydrogen). Similarly, in the preferred compounds of the  
 18 invention there is no  $R_3$  substituent (other than hydrogen). The  $R_1$   
 19 substituent of the compounds of the invention is preferably lower alkyl,  
 20 and even more preferably methyl.

21 Preferred Z groups are:

22  $-(CR_1=CR_1)_{n'}$  where  $n'$  is 0, 1, or 3 (when  $n'$  is 3 then Y  
 23 represents a direct valence bond between the  $-(CR_1=CR_1)_{n'}$  group and  
 24 the  $-A-B$  group),

25  $-N=N-$ ,

26  $-CO-CR_1=CR_1-$ ,

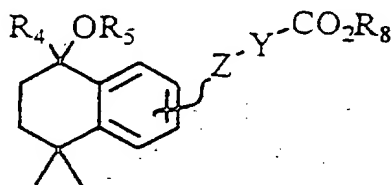
27  $-COO-$ , and

28  $-CONH-$ .

29 Referring now specifically to compounds in accordance with  
 30 **Formula 1**, compounds in these series are preferred where  $X_2$  is O, the  
 31  $R_4$  group is H, lower alkyl, or  $CH_2COOR_8$ , and  $R_5$  is H,  $Si(C_{1-6}alkyl)_3$ ,

1 COR<sub>14</sub>, C(R<sub>15</sub>)(R<sub>16</sub>)X<sub>2</sub>R<sub>17</sub>, COCH<sub>3</sub> for COR<sub>14</sub>, and CH<sub>2</sub>OCH<sub>3</sub> and 2-(1-  
 2 tetrahydropyranyl) for the C(R<sub>15</sub>)(R<sub>16</sub>)X<sub>2</sub>R<sub>17</sub> group are particularly  
 3 preferred.

4 The most preferred compounds in accordance with Formula 1 are  
 5 listed below in the Table for Formula 1A and with reference to that  
 6 formula.



15 Formula 1A

16 TABLE For Formula 1A

17  
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| Compound No. | R <sub>4</sub>        | R <sub>5</sub>                   | Z                    | Y   | R <sub>8</sub> | Configuration, When Applicable and or position of substituent Z |
|--------------|-----------------------|----------------------------------|----------------------|---|----------------|---|
| A-32         | CH <sub>2</sub> COOEt | H                                | CH=CH                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>  | Et             | 2   |
| B-3          | H                     | t-butyl                          | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup> | Et             | 2   |
|              |                       | dimethylsilyl                    |                      |   |                |   |
| B-4          | H                     | H                                | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup> | Et             | 2   |
| B-5          | H                     | H                                | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup> | H              | 2   |
| B-8          | H                     | CH <sub>2</sub> OCH <sub>3</sub> | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup> | Et             | 2   |
| B-9          | H                     | CH <sub>2</sub> OCH <sub>3</sub> | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup> | H              | 2   |
| B-10         | H                     | COCH <sub>3</sub>                | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup> | Et             | 2   |
| C-13         | H                     | H                                | polyene <sup>4</sup> | ---   | Et             | 2   |
| C-19         | H                     | H                                | polyene <sup>4</sup> | ---   | H              | 2   |
| C-26         | H                     | CH <sub>2</sub> OCH <sub>3</sub> | polyene <sup>4</sup> | ---   | Et             | 2   |
| C-27         | H                     | CH <sub>2</sub> OCH <sub>3</sub> | polyene <sup>4</sup> | ---   | H              | 2   |
| C-29         | H                     | THP <sup>3</sup>                 | polyene <sup>4</sup> | ---   | Et             | 2   |
| C-31         | H                     | THP <sup>3</sup>                 | polyene <sup>4</sup> | ---   | H              | 2   |

|    |      |                       |                                  |           |  |   |   |
|----|------|-----------------------|----------------------------------|-----------|--|---|---|
| 1  | D-1  | CH <sub>2</sub> COOEt | H                                | -N=N-     | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 2  | D-5  | H                     | H                                | -N=N-     | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 3  | D-6  | H                     | CH <sub>2</sub> OCH <sub>3</sub> | -N=N-     | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 4  | D-7  | H                     | CH <sub>2</sub> OCH <sub>3</sub> | -N=N      | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 5  | D-27 | H                     | CH <sub>2</sub> OCH <sub>3</sub> | CO-CH=CH- | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 3 |
| 6  | E-32 | H                     | H                                | CO-NH     | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 7  | E-33 | H                     | H                                | -CO-NH-   | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 8  | E-34 | H                     | CH <sub>2</sub> OCH <sub>3</sub> | -CO-NH-   | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 9  | E-35 | H                     | CH <sub>2</sub> OCH <sub>3</sub> | -CO-NH-   | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 10 | E-37 | H                     | H                                | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | (CH <sub>2</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>2</sub> | 2 |
| 11 | E-38 | H                     | CH <sub>2</sub> OCH <sub>3</sub> | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | (CH <sub>2</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>2</sub> | 2 |
| 12 | E-39 | H                     | CH <sub>2</sub> OCH <sub>3</sub> | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 13 | E-40 | H                     | H                                | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 14 | E-41 | H                     | CH <sub>2</sub> OCH <sub>3</sub> | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 15 | E-49 | CH <sub>2</sub> COOEt | COCH <sub>3</sub>                | -CO-NH-   | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 16 | E-54 | CH <sub>2</sub> COOEt | H                                | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 17 | E-56 | H                     | THP <sup>3</sup>                 | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 18 | E-60 | H                     | THP <sup>3</sup>                 | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Benzyl  | 2 |
| 19 | E-64 | H                     | THP <sup>3</sup>                 | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 20 | E-65 | H                     | THP <sup>3</sup>                 | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 21 | E-66 | H                     | THP <sup>3</sup>                 | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 22 | E-67 | H                     | THP <sup>3</sup>                 | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 23 | E-70 | H                     | THP <sup>3</sup>                 | -CO-NH    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 24 | E-72 | H                     | THP <sup>3</sup>                 | -CO-NH-   | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2 |
| 25 | E-74 | H                     | THP <sup>3</sup>                 | -CO-NH    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 26 | E-75 | H                     | THP <sup>3</sup>                 | -CO-NH    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 27 | E-76 | H                     | THP <sup>3</sup>                 | -CO-NH    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 28 | E-77 | H                     | THP <sup>3</sup>                 | -CO-NH    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2 |
| 29 | E-82 | H                     | H                                | -CO-O-    | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Benzyl  | 2 |

- 30
- 31 <sup>1</sup> 1,4-C<sub>6</sub>H<sub>4</sub> stands for 1,4-substituted phenyl
- 32 <sup>2</sup> 2,6-C<sub>10</sub>H<sub>6</sub> stands for 2,6-substituted naphthalene
- 33 <sup>3</sup> THP stands for 2-(1-tetrahydropyranyl).
- 34 <sup>4</sup> polyene stands for -C(CH<sub>3</sub>)=CH-CH=CH-(CH<sub>3</sub>)=CH-
- 35

36 Referring now to compounds in accordance with Formula 2,

37 compounds in these series are preferred where the two X<sub>2</sub>R<sub>18</sub> jointly

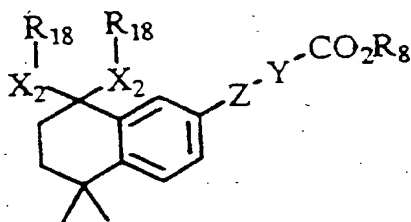
38 symbolize an oxo (=O) group, or where the two X<sub>2</sub>R<sub>18</sub> groups each

39 symbolize an S-alkyl group, or where where the two X<sub>2</sub>R<sub>18</sub> groups jointly

40 symbolize two sulphur atoms connected with a alkylidene bridge as in a

41 cyclic thioketal function.

The most preferred compounds in accordance with Formula 2 are listed below in the Table for Formula 2A and with reference to that formula.



Formula 2A

TABLE FOR FORMULA 2A

| Compound | No. | X <sub>2</sub> | R <sub>18</sub>                              | Z                    | Y   | R <sub>8</sub>  |
|----------|-----|----------------|--|----------------------|---|---|
| A-2      |     | O <sup>1</sup> | --   | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | Et  |
| A-2a     |     | O <sup>1</sup> | --   | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | H   |
| A-23     |     | S              | (CH <sub>2</sub> ) <sub>3</sub> <sup>3</sup> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | Et  |
| A-24     |     | S              | (CH <sub>2</sub> ) <sub>3</sub> <sup>3</sup> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | H   |
| B-1      |     | --             | H <sup>4</sup>                               | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup> | Et  |
| B-2      |     | --             | H <sup>4</sup>                               | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup> | H   |
| B-6      |     | O <sup>1</sup> | --   | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup> | Et  |
| B-7      |     | O <sup>1</sup> | --   | ---                  | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>5</sup> | H   |
| C-5      |     | O <sup>1</sup> | --   | polyene <sup>6</sup> | --  | Et  |
| D-10     |     | O <sup>1</sup> | --   | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | Et  |
| E-28     |     | O <sup>1</sup> | --   | -CO-NH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | Et  |
| E-29     |     | O <sup>1</sup> | --   | -CO-NH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | H   |
| E-36     |     | O <sup>1</sup> | --   | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | (CH <sub>2</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>3</sub> |
| E-44     |     | O <sup>1</sup> | --   | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | Et  |
| E-81     |     | O <sup>1</sup> | --   | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>2</sup>  | benzyl  |

1     <sup>1</sup> The two  $X_2-R_{18}$  jointly symbolize an oxo ( $=O$ ) group;

2     <sup>2</sup> 1,4- $C_6H_4$  stands for 1,4-substituted phenyl;

3     <sup>3</sup> The three methylene groups form a propylene bridge;

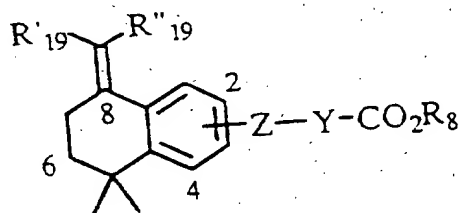
4     <sup>4</sup> Each of the two  $X_2R_{18}$  groups is H;

5     <sup>5</sup> 2,6- $C_{10}H_6$  stands for 2,6-substituted naphthalene.

6     <sup>6</sup> polyene stands for  $-C(CH_3)=CH-CH=CH-(CH_3)=CH-$

7           Compounds in accordance with **Formula 3** are preferred where  
8     the  $R_{19}$  groups are alkyl, especially lower alkyl, most preferably methyl  
9     or ethyl, where the two  $R_{19}$  groups together with the methylenedene  
10    carbon form a 5 or 6 membered ring, and where the  $R_{19}$  groups are  
11    phenyl. Compounds are also preferred in accordance with this formula  
12    where one of the  $R_{19}$  groups is  $COOR_8$ , or  $COOH$ , and the other is H.

13           The most preferred compounds in accordance with **Formula 3** are  
14    listed below in the **Table for Formula 3A** and with reference to that  
15    formula.



26           **Formula 3A**

TABLE FOR FORMULA 3A

| Compound No. | R <sub>19'</sub>                             | R <sub>19''</sub>               | Z                    | Y  | R <sub>8</sub>                                    | Configuration when applicable and/or position of substituent |
|--------------|--|---------------------------------|----------------------|--|---|--|
| A-25         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2  |
| A-26         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2  |
| A-27         | CH <sub>2</sub> CH <sub>3</sub>              | CH <sub>2</sub> CH <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2  |
| A-28         | CH <sub>2</sub> CH <sub>3</sub>              | CH <sub>2</sub> CH <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2  |
| A-29         | (CH <sub>2</sub> ) <sub>5</sub> <sup>2</sup> | --                              | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2  |
| A-31         | (CH <sub>2</sub> ) <sub>5</sub> <sup>2</sup> | --                              | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2  |
| C-17a        | COOEt  | H                               | polyene <sup>3</sup> | --   | Et  | 2, <i>anti</i>   |
| C-17b        | COOEt  | H                               | polyene <sup>3</sup> | --   | Et  | 2, <i>syn</i>  |
| C-36         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | polyene <sup>3</sup> | --   | Et  | 2  |
| C-41         | phenyl                                       | phenyl                          | polyene <sup>3</sup> | --   | Et  | 2  |
| D-2a         | COOEt  | H                               | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2  |
| D-23         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -CO-CH=CH-           | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 3  |
| E-13         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | CH <sub>2</sub> CH <sub>2</sub> SiMe <sub>3</sub> | 2  |
| E-14         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2  |
| E-15         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2  |
| E-16         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2  |
| E-17         | CH <sub>3</sub>                              | CH <sub>3</sub>                 | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2  |
| E-50a        | COOEt  | H                               | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2  |
| E-52         | COOH   | H                               | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2, <i>cis</i>  |
| E-53         | COOH   | H                               | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2, <i>trans</i>  |

<sup>1</sup> 1,4-C<sub>6</sub>H<sub>4</sub> stands for 1,4-substituted phenyl

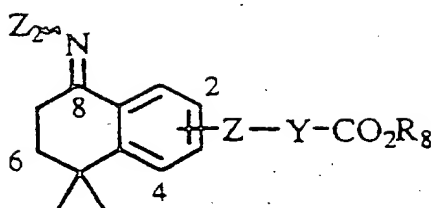
<sup>2</sup> The 5-methylene groups together with the methylenedene group form a 6-membered ring.

<sup>3</sup> polyene stands for C(CH<sub>3</sub>)=CH-CH=CH-C(CH<sub>3</sub>)=CH-

Referring now to compounds in accordance with Formula 4,

compounds in these series are preferred where the Z<sub>2</sub> group is O-lower alkyl, especially OCH<sub>3</sub> or OCH<sub>2</sub>CH<sub>3</sub>. The most preferred

compounds in accordance with Formula 4 are listed below in the Table for Formula 4A and with reference to that formula.



Formula 4A

TABLE FOR FORMULA 4A

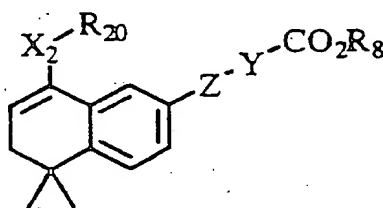
|    | Compound | Z <sub>2</sub>                   | Z                    | Y  | R <sub>8</sub> | Position of Z<br>Substituent<br>and/or<br>configuration as<br>Applicable |
|----|----------|----------------------------------|----------------------|--|----------------|--|
| 14 | No.      |                                  |                      |  |                |  |
| 17 | A-3      | OCH <sub>3</sub>                 | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | Et             | 2, <i>anti</i>   |
| 18 | A-4      | OCH <sub>3</sub>                 | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | H              | 2, <i>anti</i>   |
| 19 | A-5      | OCH <sub>2</sub> CH <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | Et             | 2, <i>anti</i>   |
| 20 | A-6      | OCH <sub>2</sub> CH <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | H              | 2, <i>anti</i>   |
| 21 | A-7      | OH                               | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | Et             | 2, <i>anti</i>   |
| 22 | A-8      | OH                               | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | H              | 2, <i>anti</i>   |
| 23 | B-11     | OCH <sub>3</sub>                 | --                   | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup>                                    | Et             | 2, <i>anti</i>   |
| 24 | B-12     | OCH <sub>3</sub>                 | --                   | 2,6-C <sub>10</sub> H <sub>6</sub> <sup>2</sup>                                    | H              | 2, <i>anti</i>   |
| 25 | C-6      | OCH <sub>3</sub>                 | polyene <sup>3</sup> | --   | Et             | 2, <i>anti</i>   |
| 26 | C-22a    | OCH <sub>2</sub> CH <sub>3</sub> | polyene <sup>3</sup> | --   | Et             | 2, <i>syn</i>  |
| 27 | C-22b    | OCH <sub>2</sub> CH <sub>3</sub> | polyene <sup>3</sup> | --   | Et             | 2, <i>anti</i>   |
| 28 | C-24     | OCH <sub>2</sub> CH <sub>3</sub> | polyene <sup>3</sup> | --   | H              | 2, <i>syn</i>  |
| 29 | C-25     | OCH <sub>2</sub> CH <sub>3</sub> | polyene <sup>3</sup> | --   | H              | 2, <i>anti</i>   |
| 30 | D-3      | OCH <sub>3</sub>                 | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | Et             | 2, <i>anti</i>   |
| 31 | D-4      | OCH <sub>3</sub>                 | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | H              | 2, <i>anti</i>   |
| 32 | D-29     | OCH <sub>3</sub>                 | -CO-CH=CH-           | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | H              | 3  |
| 33 | E-30     | OCH <sub>3</sub>                 | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | Et             | 2, <i>anti</i>   |
| 34 | E-31     | OCH <sub>3</sub>                 | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | H              | 2, <i>anti</i>   |
| 35 | E-42     | OCH <sub>3</sub>                 | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> (CH <sub>3</sub> )SiMe <sub>3</sub> |                | 2, <i>anti</i>   |
| 36 | E-43     | OCH <sub>3</sub>                 | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | H              | 2, <i>anti</i>   |
| 37 | E-46     | OCH <sub>3</sub>                 | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup>                                     | Et             | 2, <i>anti</i>   |

<sup>1</sup> stands for 1,4-substituted phenyl<sup>2</sup> stands for 2,6-substituted naphthyl<sup>3</sup> polyene stands for C(CH<sub>3</sub>)=CH-CH=CH-C(CH<sub>3</sub>)=CH-



Compounds in accordance with **Formula 5** are preferred where the  $R_{20}$  group is lower alkyl, phenyl or  $SO_2CF_3$ .

The most preferred compounds in accordance with **Formula 5** are listed below in the **Table for Formula 5A** and with reference to that formula.



**Formula 5A**

**TABLE FOR FORMULA 5A**

|    |          |                 |                                 |                      |  |                |
|----|----------|-----------------|---------------------------------|----------------------|--|----------------|
| 14 | Compound |                 |                                 |                      |  |                |
| 15 | No.      | X <sub>2</sub>  | R <sub>20</sub>                 | Z                    | Y  | R <sub>8</sub> |
| 16 | A-9      | O               | SO <sub>2</sub> CF <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et             |
| 17 | A-16     | S               | phenyl                          | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et             |
| 18 | A-18     | S               | phenyl                          | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H              |
| 19 | A-17     | SO <sub>2</sub> | phenyl                          | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et             |
| 20 | A-19     | SO <sub>2</sub> | phenyl                          | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H              |
| 21 | A-20     | S               | CH <sub>2</sub> CH <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et             |
| 22 | A-21     | S               | CH <sub>2</sub> CH <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H              |
| 23 | A-22     | SO <sub>2</sub> | CH <sub>2</sub> CH <sub>3</sub> | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H              |
| 24 | C-10     | S               | phenyl                          | polyene <sup>2</sup> | --   | Et             |
| 25 | C-11     | SO <sub>2</sub> | phenyl                          | polyenc <sup>2</sup> | --   | Et             |
| 26 | C-12     | SO              | phenyl                          | polyene <sup>2</sup> | --   | Et             |
| 27 | C-14     | O               | SO <sub>2</sub> CF <sub>3</sub> | polyene <sup>2</sup> | --   | Et             |
| 28 | C-28     | O               | trimethylsilyl                  | polyene <sup>2</sup> | --   | Et             |
| 29 | D-11     | O               | SO <sub>2</sub> CF <sub>3</sub> | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et             |
| 30 | E-20     | S               | phenyl                          | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et             |
| 31 | E-21     | S               | phenyl                          | -CONH-               | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H              |

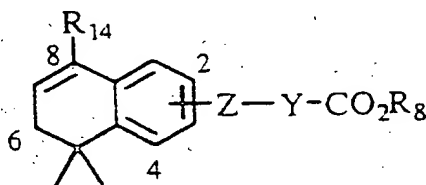
|   |      |                 |        |        |  |   |
|---|------|-----------------|--------|--------|--|---|
| 1 | E-22 | SO <sub>2</sub> | phenyl | -CONH- | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   |
| 2 | E-23 | S               | phenyl | -COO-  | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  |
| 3 | E-24 | SO <sub>2</sub> | phenyl | -COO-  | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  |
| 4 | E-25 | S               | phenyl | -COO-  | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | (CH <sub>3</sub> ) <sub>2</sub> Si(CH <sub>3</sub> ) <sub>3</sub> |
| 5 | E-26 | S               | phenyl | -COO-  | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   |
| 6 | E-27 | SO <sub>2</sub> | phenyl | -COO-  | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   |

7 <sup>1</sup> stands for 1,4-substituted phenyl

8 <sup>2</sup> polyene stands for C(CH<sub>3</sub>)=CH-CH=CH-(CH<sub>3</sub>)=CH

9 Referring now to compounds in accordance with **Formula 6**,  
 10 compounds in these series are preferred where the **R<sub>14</sub>** group is  
 11 thiazolyl, more preferably 2-thiazolyl, thienyl, more preferably 2-thienyl,  
 12 branched chain lower alkyl, more preferably *t*-butyl, or where **R<sub>14</sub>** is  
 13 CH<sub>2</sub>COOR<sub>8</sub> or CH<sub>2</sub>COOH.

14 The most preferred compounds in accordance with **Formula 6** are  
 15 listed below in the **Table for Formula 6A** and with reference to that  
 16 formula.



24 **Formula 6A**

TABLE FOR FORMULA 6A

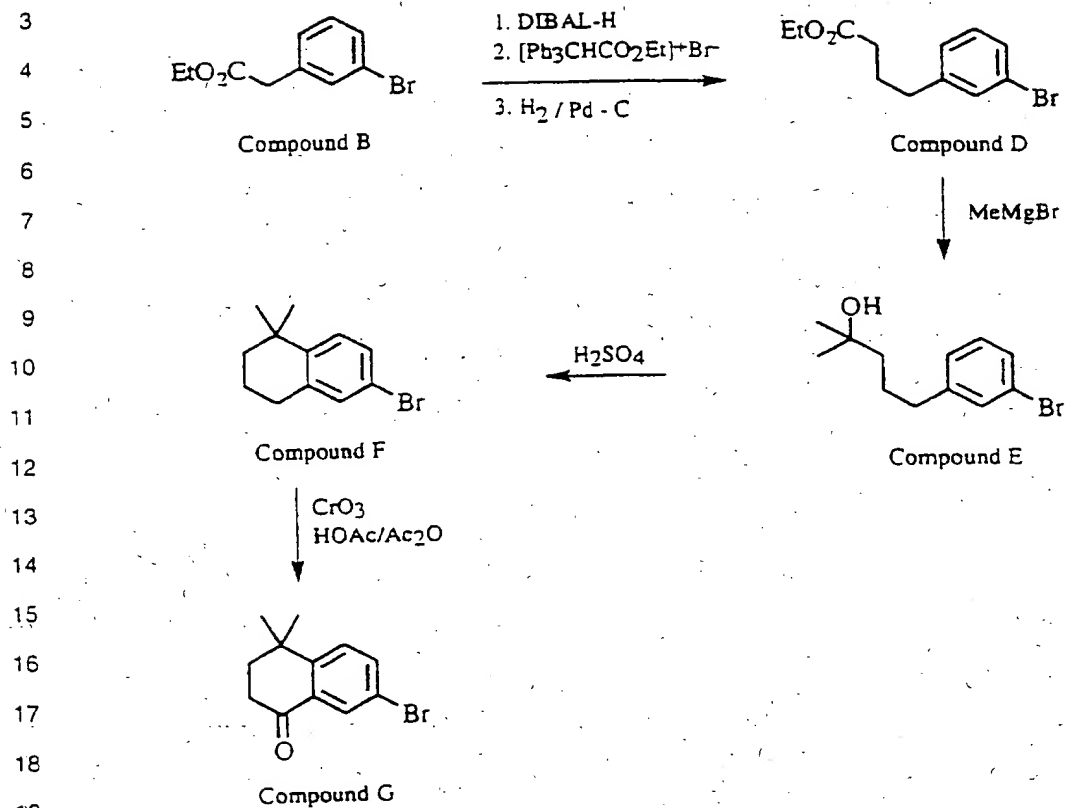
| Compound No. | R <sub>14</sub>        | Z                    | Y  | R <sub>8</sub>                                    | Position of Z Substituent |
|--------------|------------------------|----------------------|--|---|---------------------------|
|              |                        |                      |  |   |                           |
| A-10         | 2-thiazolyl            | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| A-12         | 2-thiazolyl            | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2                         |
| A-13         | 2-thienyl              | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| A-15         | 2-thienyl              | -CH=CH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2                         |
| C-15         | 2-thienyl              | polyene <sup>2</sup> | --   | Et  | 2                         |
| C-20         | 2-thienyl              | polyene <sup>2</sup> | --   | H   | 2                         |
| C-46         | t-butyl                | polyene <sup>2</sup> | --   | Et  | 2                         |
| D-2b         | CH <sub>2</sub> COOEt  | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| D-12         | 2-thienyl              | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| D-13         | 2-thienyl              | -N=N-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2                         |
| D-18         | CH <sub>2</sub> COOEt  | CO-CH=CH-            | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 3                         |
| D-20         | t-butyl                | -CO-CH=CH-           | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 3                         |
| D-34         | 2-thienyl              | CO-CH=CH-            | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 3                         |
| E-7          | 2-thienyl              | -CO-NH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| E-8          | 2-thienyl              | -CO-NH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2                         |
| E-9          | 2-thienyl              | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| E-10         | 2-thienyl              | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | (CH <sub>2</sub> ) <sub>3</sub> SiMe <sub>3</sub> | 2                         |
| E-11         | 2-thienyl              | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2                         |
| E-50b        | CH <sub>2</sub> -COOEt | -CO-NH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| E-55         | CH <sub>2</sub> COOEt  | -COO-                | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| E-79         | t-butyl                | -CO-NH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | Et  | 2                         |
| E-80         | t-butyl                | -CO-NH-              | 1,4-C <sub>6</sub> H <sub>4</sub> <sup>1</sup> | H   | 2                         |

<sup>1</sup> stands for 1,4-substituted phenyl

<sup>2</sup> polyene stands for C(CH<sub>3</sub>)=CH-CH=CH-C(CH<sub>3</sub>)=CH-

The compounds of this invention can be made by the general procedures outlined above under the title "GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY". The following chemical pathways represent the presently contemplated best synthetic routes to certain exemplary compounds of the invention illustrated here. However, the synthetic chemist will readily appreciate that the conditions set out here for these specific embodiments can be generalized to any and all of the compounds represented by Formulas 1

1 through 6.



### Reaction Scheme 1

Important starting materials for the synthesis of the preferred compounds of the invention are

6-bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (Compound F),

7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1-one (Compound G), and

the isomeric bromo compound,

6-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound H).

Compound G can be obtained as described in *J. Med. Chem.* 1995, 38, 4764 - 4767, and as shown in Reaction Scheme 1. Thus, referring now specifically to Reaction Scheme 1, ethyl 3-bromophenylacetate

(Compound B, made by esterification of 3-bromophenylacetic acid) is

reduced with diisobutylaluminum hydride (DIBAL H) to yield

1 (3-bromophenyl)acetaldehyde. (3-Bromophenyl)acetaldehyde is reacted  
2 in a *Wittig* reaction with (carbethoxymethylene)triphenylphosphorane to  
3 provide a mixture of E and Z ethyl 4-(3-bromophenyl)but-2-enoates.  
4 The latter compounds are hydrogenated to yield ethyl  
5 4-(3-bromophenyl)butanoate (**Compound D**). **Compound D** is reacted  
6 with the Grignard reagent derived from methylbromide to give the  
7 tertiary alcohol 5-(3-bromophenyl)-2-methylpentan-2-ol (**Compound E**)  
8 (It should be apparent to those skilled in the art, that the choice of the  
9 Grignard reagent used in this reaction step determines the nature of the  
10 R<sub>1</sub> substituent in the resulting compounds of the invention.) **Compound**  
11 **E** is then treated with acid to cyclize it and to form  
12 6-bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (**Compound F**).  
13 **Compound F** is oxidized with chromium trioxide to yield  
14 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**).  
15 The isomeric compound,  
16 6-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound H**)  
17 can be obtained, starting with ethyl (4-bromophenyl)acetate, in  
18 accordance with the sequence of reactions illustrated in **Reaction**  
19 **Scheme 1** for **Compound G**.  
20 6-Bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound H**)  
21 can also be obtained in accordance with the published literature  
22 procedure: Mathur et al. Tetrahedron, 41, 1509-1516 (1985).

23 Another important starting material for the synthesis of several  
24 preferred compounds of the invention is 3,4-dihydro-4,4-dimethyl-7-  
25 aminonaphthalen-1(2H)-one (**Compound D9**) which is prepared from  
26 the known 3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one, by nitration  
27 and subsequent catalytic reduction of the intermediate 3,4-dihydro-4,4-  
28 dimethyl-7-nitronaphthalen-1(2H)-one (**Compound D8**), as is described  
29 in the enclosed description of specific examples.

30 Still other important starting materials for the synthesis of several  
31 preferred compounds of the invention are the isomeric 3,4-dihydro-4,4-

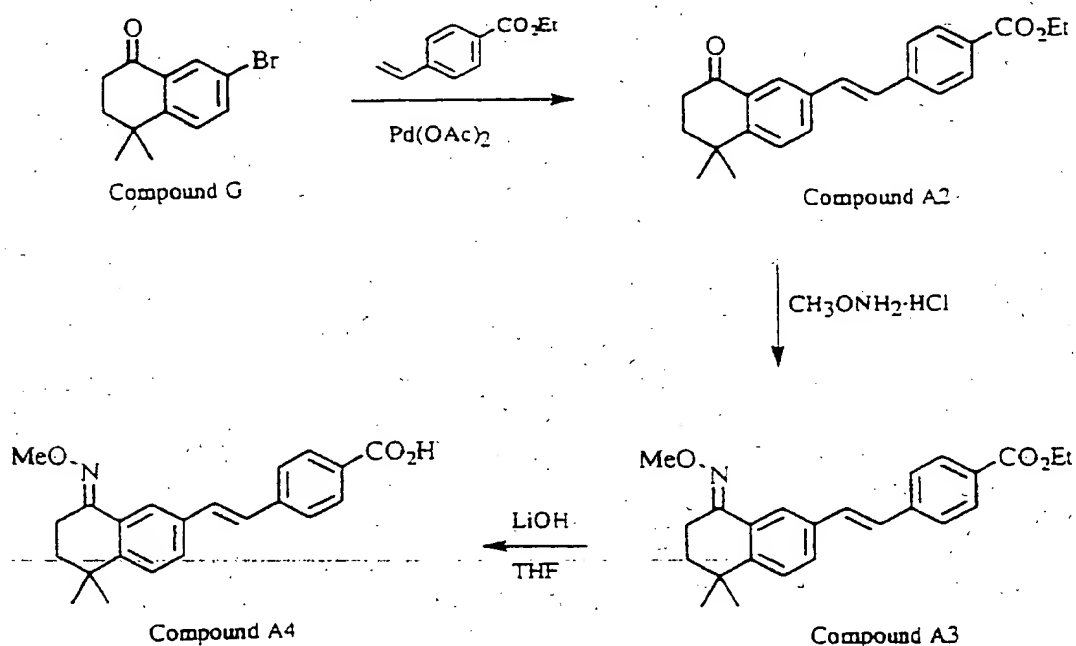
1 dimethyl-7-acetyl-naphthalen-1(2H)-one (**Compound D14a**); and 3,4-  
2 dihydro-4,4-dimethyl-6-acetyl-naphthalen-1(2H)-one (**Compound D14b**).  
3 These are prepared by reacting 1,2,3,4-tetrahydro-1,1-  
4 dimethylnaphthalene with acetyl chloride in a Friedel-Crafts type  
5 reaction, followed by oxidation with chromium trioxide of the isomeric  
6 acetyl derivatives. These compounds can also be obtained by an  
7 alternative procedure from **Compounds G** and **H** respectively. The  
8 experimental conditions of these preparations are disclosed in the  
9 description of the specific examples.

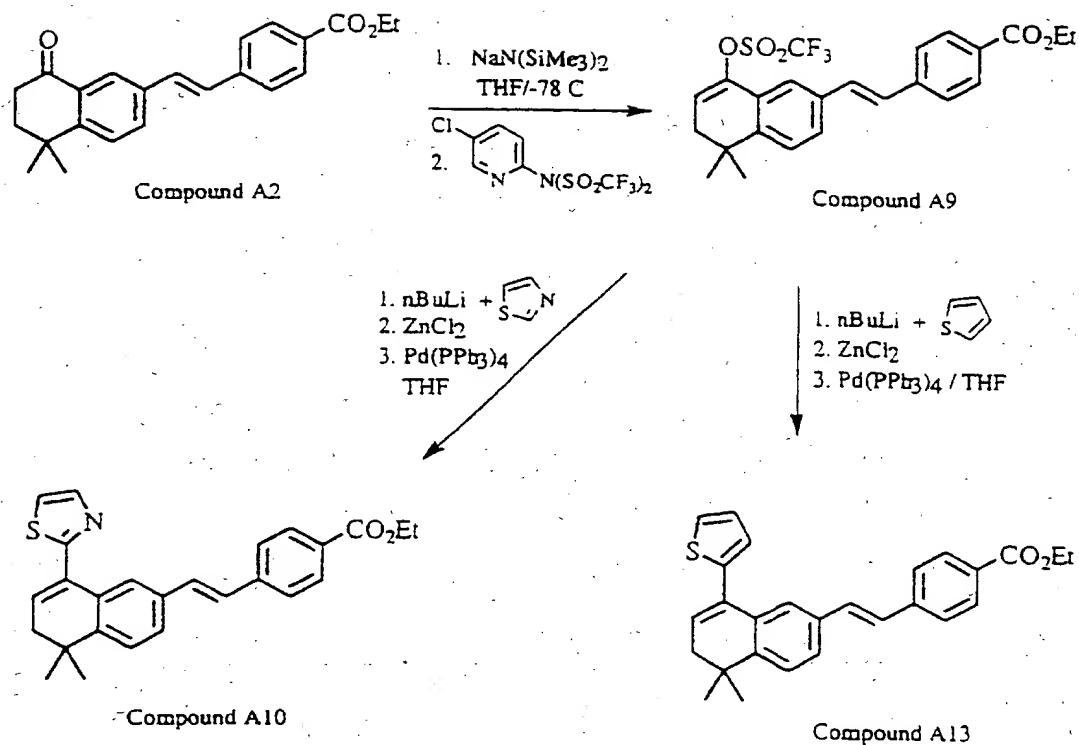
10 Yet another important starting material for the synthesis of  
11 several preferred compounds of the invention is methyl 5,5-dimethyl-5,6-  
12 dihydro-naphthalen-8(7H)-one-2-carboxylate (**Compound E2**) which can  
13 be made by reaction of  
14 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1-one (**Compound G**) with  
15 CO<sub>2</sub> in the presence of *t*-butyl lithium, but is more advantageously  
16 prepared in the presence of palladium(II)-  
17 bis(triphenylphosphine)chloride and 1,3-bis(diphenylphosphino)propane  
18 catalysts by reaction with carbonmonoxide and methanol, as is described  
19 in the specific examples.

20 Referring now to **Reaction Scheme 2** the synthesis of preferred  
21 examples of compounds of the invention are described, where the **Z**  
22 group, with reference to **Formulas 1 - 6** is -CH=CH-. Compounds of  
23 this type of the invention are advantageously obtained in a direct  
24 coupling reaction between an ethenyl compound such as ethyl 4-  
25 vinylbenzoate, and a 6- or 7-bromonaphthalene-1(2H)-one derivative,  
26 such as **Compound G** or **Compound H** in a reaction commonly known  
27 as the *Heck* reaction. **Reaction Scheme 2** exemplifies this reaction with  
28 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one- (**Compound G**)  
29 as the starting material. A general formula for the ethenyl compounds  
30 which are suitable as reagents in the *Heck* reaction to provide these type  
31 of compounds of the invention is CH<sub>2</sub>=CH<sub>2</sub>-Y(R<sub>2</sub>)-A-B where the

1 symbols have the same meaning as defined in connection with Formulas  
2 1 - 6. These compounds are readily available in accordance with the  
3 chemical literature, or otherwise in accordance with state-of-the-art.  
4 The *Heck* reaction is well known in the art, and is usually conducted in  
5 a basic solvent, such as triethylamine, in the presence of a phosphine  
6 catalyst (such as tris(2-methylphenyl)phosphine or tri-*O*-tolylphosphine)  
7 in the presence of palladium(II)acetate catalyst.

8 Those skilled in the art will readily understand that the  
9 compounds of the invention which have an ethylene (-CH=CH-) or  
10 substituted ethylene (-CR<sub>1</sub>=CR<sub>1</sub>-) linking group can also be made by a  
11 *Wittig* or like (*Horner Emmons*) reactions, which are *per se* well known  
12 in the art. Those skilled in the art will also readily understand that the  
13 reaction sequence shown in **Reaction Scheme 2** can be readily adapted  
14 for compounds where the tetrahydronaphthalene (or other rings within  
15 the scopes of **Formulas 1 - 6**) have R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> substituents other than  
16 specifically shown in this reaction scheme.

**Reaction Scheme 2**



### Reaction Scheme 2 (continued)

Thus in the example shown in **Reaction Scheme 2**

7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**) is reacted with ethyl 4-vinylbenzoate to yield ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethylnaphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (**Compound A2**). Ethyl 4-vinylbenzoate is available in accordance with the chemical literature, *Can. J. Chem* (1973) **51**, 897-914, which is expressly incorporated herein by reference. **Compound A2** is an example for the compounds of the present invention within the scope of **Formula 2**. **Compound A2** is reacted with methoxylamine hydrochloride in an



1 alcoholic solvent (such as ethanol) in the presence of sodium acetate to  
2 yield the methyl oxime, ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-  
3 *anti*-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoate (**Compound**  
4 **A3**). **Compound A3** can be saponified by treatment with base, such as  
5 LiOH, to provide the free carboxylic acid, (E)-4-[2-(5,5-dimethyl-5,6,-  
6 dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoic  
7 acid (**Compound A4**). **Compounds A3** and **A4** are compounds of the  
8 invention within the scope of **Formula 4**. The conditions for the  
9 saponification of **Compound A3** to provide **Compounds A4** serve as  
10 example for several saponification reactions which yield several  
11 compounds of the invention where the **B** group of **Formulas 1 - 6** is a  
12 free carboxylic acid (COOH), or salt thereof.

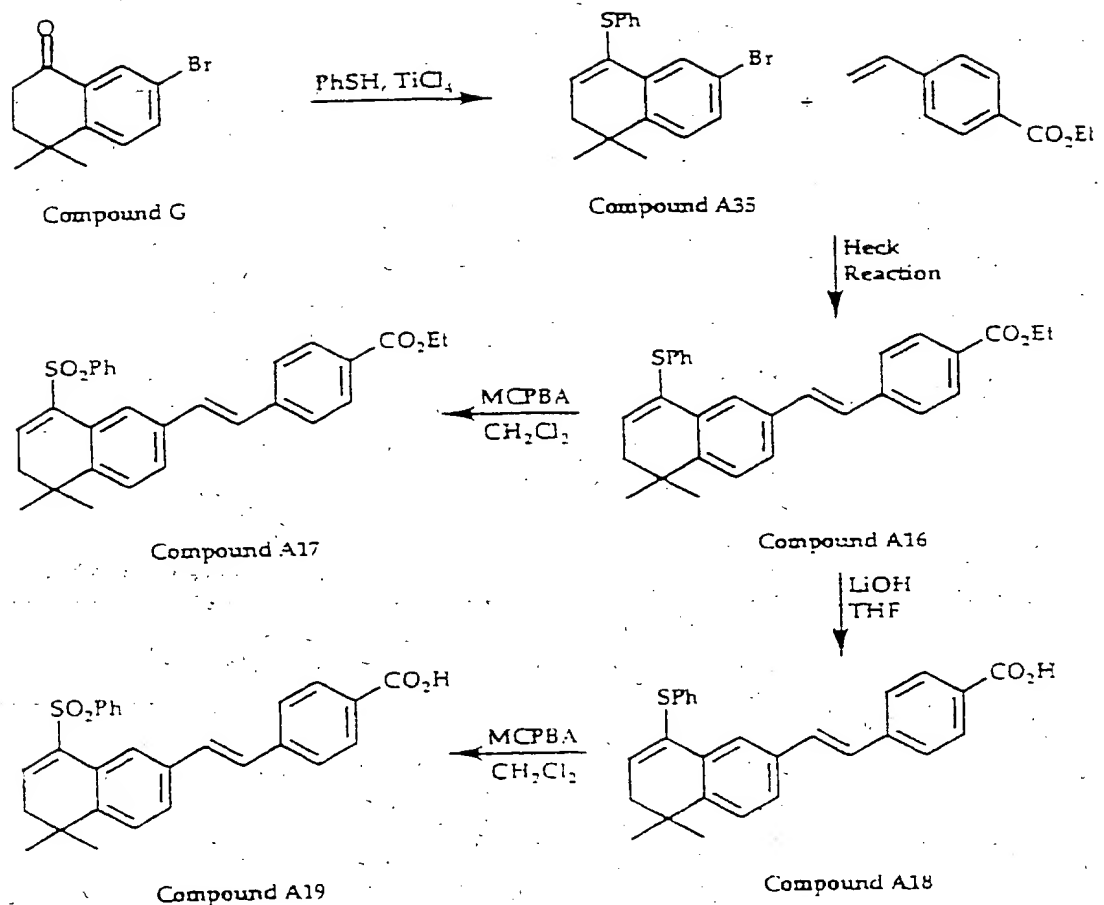
13 Instead of methoxylamine hydrochloride, hydroxylamine  
14 hydrochloride, or ethoxylamine hydrochloride or other analogous  
15 reagents can be used to obtain the oximes or other *O*-alkyl, *O*-aryl  
16 analogs of **Compounds A3** and **A4**, within the scope of **Formula 4**.  
17 Generally speaking and with reference to **Formula 4**, the oxo  
18 compounds, such as **Compound A2** are reacted with a reagent of the  
19 formula  $\text{NH}_2\text{-Z}_2$ , where  $\text{Z}_2$  is defined as in connection with **Formula 4**.  
20 Thus, the oxo compounds analogous to **Compound A2** are reacted with  
21 a reagent of the formula  $\text{H}_2\text{N-Z}_2$  to yield compounds of **Formula 4**. As  
22 is known, when the reagent  $\text{H}_2\text{N-Z}_2$  is  $\text{NH}_2\text{OH}$  or its salt, then the  
23 reaction is the formation of an oxime. Generally speaking the oximes  
24 are readily formed by reacting the oxo compounds with hydroxylamine  
25 hydrochloride in a polar solvent, such as a lower alkanol, in the  
26 presence of a buffering agent, such as sodium acetate. The reaction can  
27 be conducted under similar conditions with a reagent of the formula  
28  $\text{NH}_2\text{OR}_1$  or its salt (such as methoxylamine hydrochloride or  
29 ethoxylamine hydrochloride as demonstrated in **Reaction Scheme 2**) to  
30 yield compounds of **Formula 4** where  $\text{Z}_1$  is  $\text{OR}_1$  ( $\text{R}_1$  is defined as in  
31 connection with **Formula 4**). When the reagent  $\text{H}_2\text{N-Z}_2$  is a primary

1 amine then the reaction is the formation of an imine. The latter  
2 reaction is usually conducted in a polar (alcoholic) solvent. Further  
3 reagents, in accordance with the general formula  $H_2NZ_2$ , are those  
4 where  $Z_2$  is  $NHCON(R_{14})_2$  (formation of semicarbazone),  $NHCSN(R_{14})_2$   
5 (formation of thiosemicarbazone) and  $N(R_{14})_2$  (formation of a  
6 hydrazone). (The symbol  $R_{14}$  is defined as in connection with **Formula**  
7 **4**.) The semicarbazones, thiosemicarbazones and hydrazones  
8 corresponding to **Formula 4** can be prepared under conditions which  
9 are well known in the art for the formation of such derivatives of  
10 ketone compounds. Usually these conditions are similar to the  
11 conditions leading to the oximes described above. Typically, the  
12 hydrochloride salt of the reagent (semicarbazide, thiosemicarbazide or  
13 hydrazide) is reacted with the oxo compound such as **Compound A2** in  
14 an alcoholic solvent, in the presence of sodium acetate.

15 Referring now again specifically to **Reaction Scheme 2**, ethyl (E)-  
16 4-[2-(5,6-dihydro-5,5-dimethylnaphthalen-8(7H)-one-2-yl)ethenyl]-  
17 benzoate (**Compound A2**) is reacted with sodium  
18 bis(trimethylsilyl)amide and 2-[N,N-bis(trifluoromethane-  
19 sulfonyl)amino]-5-chloropyridine in an inert ether type solvent, such as  
20 tetrahydrofuran, at low temperatures (-78°C and 0°C). This provides  
21 first a sodium salt intermediate which is not isolated and not shown in  
22 the reaction scheme. The reactions ultimately result in the  
23 trifluoromethylsulfonyloxy derivative ethyl (E)-4-[2-(5,6-dihydro-5,5-  
24 dimethyl-8-(trifluoromethylsulfonyl)oxy-naphthalen-2-yl)ethenyl]-  
25 benzoate (**Compound A9**). **Compound A9** is within the scope of  
26 **Formula 5** of the present invention and is also an important  
27 intermediate for the synthesis of several compounds of the invention  
28 within the scope of **Formula 6**. **Compound A9** is a  
29 trifluoromethylsulfonate derivative, which sometimes also called a  
30 "triflate" in the trade, and the  $CF_3SO_2$  group is sometimes abbreviated  
31 as "Tf" in the reaction schemes.

1       As is shown further in **Reaction Scheme 2** for the specific  
2       examples of thiazole and thiophene, respectively yielding **Compounds**  
3       **A10** and **A13**, the triflate derivative **Compound A9** is reacted with an  
4       organometal derivative derived from the compound  $R_{14}H$ , such that the  
5       formula of the organometal derivative is  $R_{14}Met$  ( $Met$  stands for  
6       monovalent metal), preferably  $R_{14}Li$ . ( $R_{14}$  is defined as in connection  
7       with **Formula 6**.) The reaction with the organometal derivative,  
8       preferably lithium derivative of the formula  $R_{14}Li$  is usually conducted in  
9       an inert ether type solvent (such as tetrahydrofuran) in the presence of  
10      zinc chloride ( $ZnCl_2$ ) and tetrakis(triphenylphosphine)palladium(0)  
11      ( $Pd(PPh_3)_4$ ). The organolithium reagent  $R_{14}Li$ , if not commercially  
12      available, can be prepared from the compound  $R_{14}H$  (or its halogen  
13      derivative  $R_{14}-X_1$  where  $X_1$  is halogen) in an ether type solvent in  
14      accordance with known practice in the art. The temperature range for  
15      the reaction between the reagent  $R_{14}Li$  and the triflate derivatives is,  
16      generally speaking in the range of approximately  $-78^\circ C$  to  $50^\circ C$ .  
17      **Compounds A10** and **A13** and their analogs can be saponified, or  
18      subjected to further transformations, such as homologation and other  
19      state-of-the-art reactions which yield homologs and derivatives in  
20      accordance with the reactions discussed above.

21       **Reaction Scheme 2** serves as an example of synthetic  
22       methodology used for preparing compounds of the present invention  
23       where the  $-Y(R_2)-A-B$  group of **Formulas 1 - 6** is linked to the  
24       tetrahydronaphthalene nucleus with the desired  $Z$  group, before the  
25       final substitution pattern is obtained by transformations of the  
26       tetrahydronaphthalene (or dihydronaphthalene) moiety.



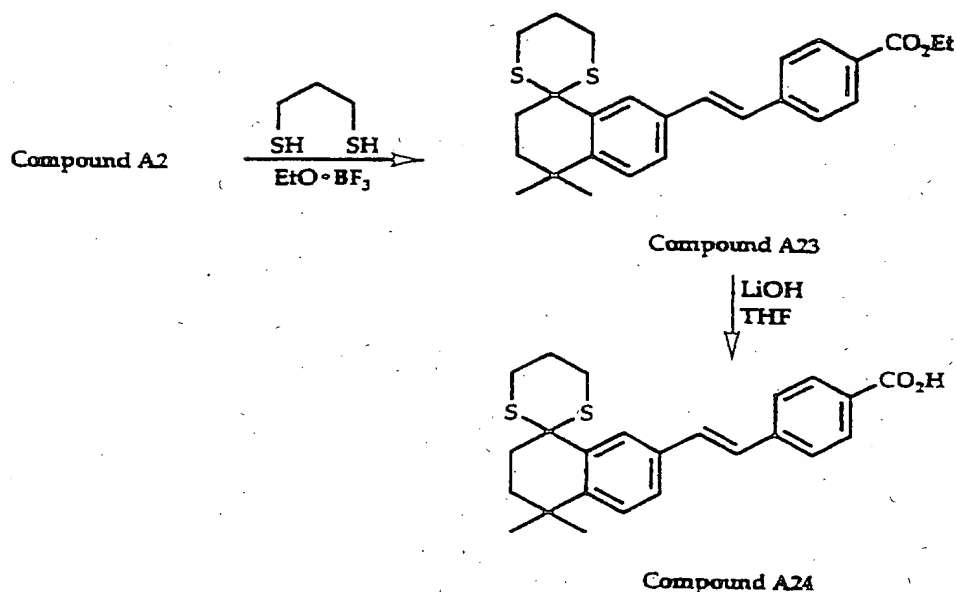
## Reaction Scheme 3

Reaction Scheme 3 provides further examples for the synthesis of compounds within the scope of Formula 5 where the linking group between the dihydronaphthalene moiety and the Y group is  $-\text{CH}=\text{CH}-$ .

In the sequence of reactions described here the oxo function of a starting tetrahydronaphthalene-one moiety is modified before a Heck coupling reaction is performed. Specifically, in the example shown in the reaction scheme,

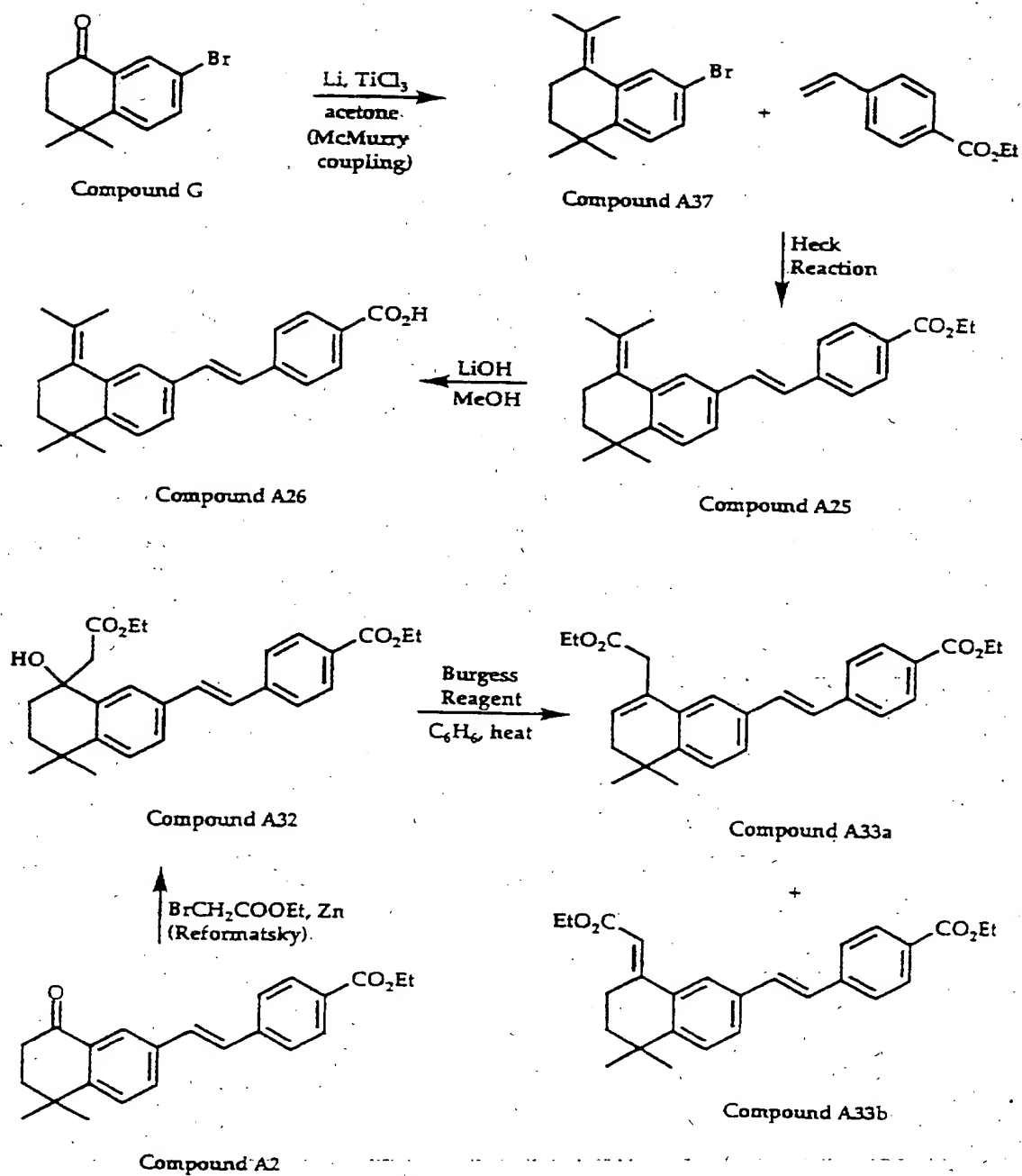
7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)

1 is reacted with thiophenol in the presence of titanium tetrachloride and  
2 triethylamine in tetrahydrofuran (THF), to provide the intermediate 4,4-  
3 dimethyl-7-bromo-1-phenylthio-3,4-dihydronaphthalene (**Compound**  
4 **A35**). A similar reaction can be performed with ethanethiol as a  
5 reagent instead of thiophenol, to yield 2-bromo-5,6-dihydro-5,5-  
6 dimethyl-8-ethylthio-naphthalene (**Compound A36**) and other analogous  
7 compounds which are not shown in the reaction scheme. **Compound**  
8 **A35** is reacted in the *Heck* reaction to yield ethyl (E)-4-[2-(5,6-dihydro-  
9 5,5-dimethyl-8-phenylthio-naphthalenyl)ethenyl] benzoate (**Compound**  
10 **A16**). **Compound A16** is saponified to yield the carboxylic acid, (E)-4-  
11 [2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-naphthalen-2-yl)ethenyl]  
12 benzoic acid (**Compound A18**), and is oxidized with *m*-  
13 chloroperoxybenzoic acid (MCPBA) to provide the corresponding  
14 phenylsulfonyl compound, ethyl (E)-4-[-2-(5,6-dihydro-5,5-dimethyl-8-  
15 (phenylsulfonyl)-naphthalenyl)ethenyl]benzoate (**Compound A17**).  
16 **Compound A18** can also be oxidized under similar conditions to provide  
17 the free carboxylic acid (or salt thereof) of the phenylsulfonyl  
18 compound, (E)-4-[-2-(5,6-dihydro-5,5-dimethyl-8-phenylsulfonyl-  
19 naphthalenyl)ethenyl]benzoic acid (**Compound A19**).



#### Reaction Scheme 4

17        **Reaction Scheme 4** discloses further examples for the preparation  
18 of compounds of the invention within the scope of **Formula 2** where the  
19 group linking the tetrahydronaphthalene and Y(R<sub>2</sub>)-A-B moieties is -  
20 CH=CH-. As is shown in the scheme, ethyl (E)-4-[2-(5,6-dihydro-5,5-  
21 dimethylnaphthalen-8(7H)-one-2-yl)ethenyl]benzoate (**Compound A2**) is  
22 reacted with 1,3-propanedithiol in the presence of borontrifluoride  
23 diethyl etherate to yield the corresponding cyclic thioketal compound,  
24 ethyl (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(1,3-dithian-2-  
25 yl)naphthalen-2-yl)ethenyl] benzoate (**Compound A23**). Other ketal  
26 and thioketal analogs of this compound, within the scope of **Formula 2**  
27 can be obtained by analogous reactions suitable for ketal and thioketal  
28 formation, which are *per se* well known in the-art. Saponification of  
29 **Compound A23** provides the corresponding free acid (or salt thereof),  
30 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(2-(1,3-dithian-2-  
31 yl)naphthalenyl)ethenyl]benzoic acid (**Compound A24**).



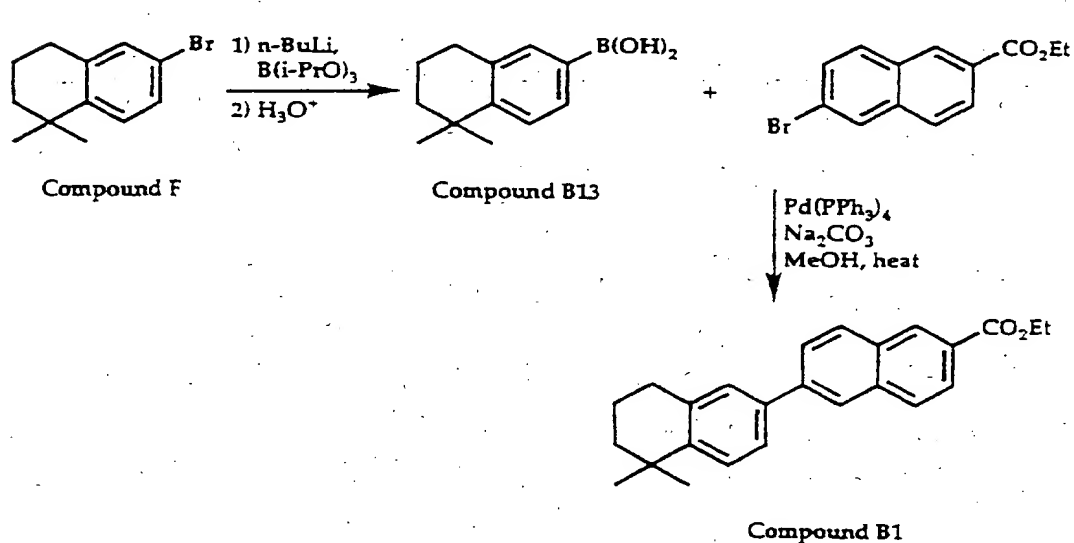
Reaction Scheme 5

1           **Reaction Scheme 5** provides examples for the synthesis of  
2 compounds of the invention within the scope of **Formula 3**. The  
3 synthesis of these compounds proceeds in accordance with methodology  
4 where the desired substituent is introduced into the  
5 tetrahydronaphthalene moiety before this moiety is coupled or linked  
6 to the desired **Z-Y(R<sub>2</sub>)-A-B** group, and in these examples also the **Z**  
7 group is -CH=CH-. Thus in accordance with this scheme,  
8 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**)  
9 is reacted in a *McMurry* coupling reaction with acetone to provide 7-  
10 bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
11 (**Compound A37**). The reaction (*McMurry* coupling) is conducted at  
12 elevated temperature in the presence of lithium metal and titanium  
13 trichloride, in an inert ether type solvent, for example in refluxing  
14 1,2-dimethoxyethane (DME). In other examples which are described in  
15 the Specific Examples, 3-pentanone, and cyclohexanone are used as  
16 ketone reagents, instead of the acetone shown in the reaction scheme.  
17 **Compound A37** is then subjected to a *Heck* coupling reaction with an  
18 ethenyl reagent such as ethyl 4-vinylbenzoate shown in the scheme, to  
19 provide ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-(propyliden-2-yl)-  
20 naphthalen-2-yl)ethenyl]benzoate (**Compound A25**). **Compound A25** is  
21 saponified under conditions described above to provide (E)-4-[2-(5,6-  
22 dihydro-5,5-dimethyl-8(7H)-(propyliden-2-yl)-naphthalen-2-yl)ethenyl]-  
23 benzoic acid (**Compound A26**).

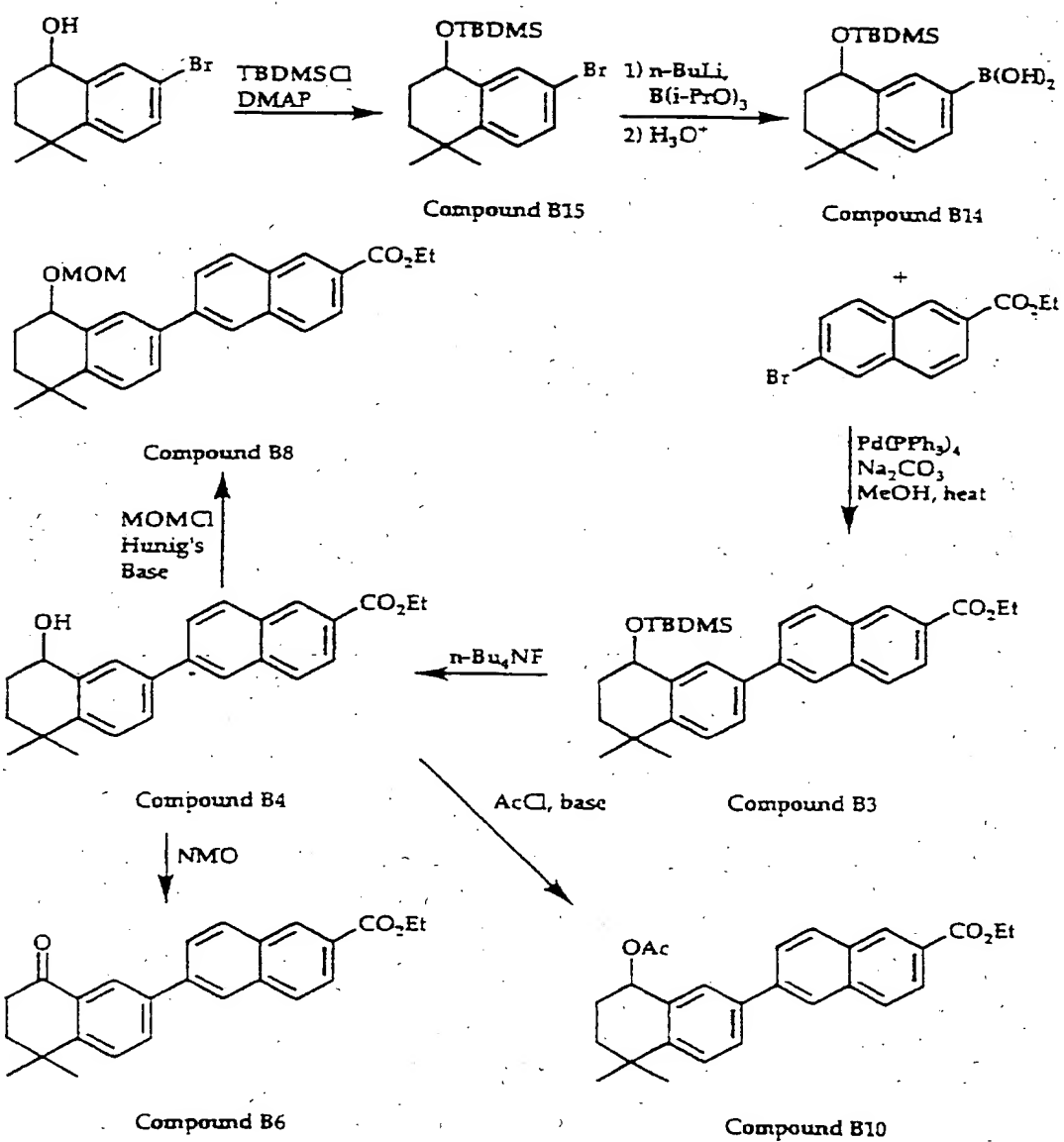
24           **Reaction Scheme 5** discloses another example for the preparation  
25 of compounds within the scope of **Formula 3**. In this example the  
26 substituent is introduced to replace the oxo function of  
27 tetrahydronaphthalene-2-one after the **Z-Y(R<sub>2</sub>)-A-B** group has already  
28 been coupled to the tetrahydronaphthalene nucleus. Thus, ethyl (E)-4-  
29 [2-(5,6-dihydro-5,5-dimethyl-naphthalen-8(7H)-one-2-yl)ethenyl]-  
30 benzoate (**Compound A2**) is reacted with ethyl bromoacetate in the  
31 presence of zinc metal in a *Reformatsky* reaction to provide (+/-) ethyl



1 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-8-  
2 (carbethoxymethyl)naphthalen-2-yl)ethenyl] benzoate (**Compound A32**).  
3 **Compound A32** is itself within the scope of the present invention, within  
4 the scope of **Formula 1**. **Compound A32** is dehydrated, as shown in the  
5 example by treatment with (methoxycarbonyl  
6 sulfamoyl)triethylammonium hydroxide (*Burgess reagent*) to yield a  
7 mixture of ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-  
8 (carbethoxymethyl)naphthalen-2-yl)ethenyl]benzoate (**Compound A33a**),  
9 and ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-*anti*  
10 (carbethoxymethylidenyl)-naphthalen-2-yl)ethenyl]benzoate (**Compound**  
11 **A33b**). **Compound A33a** is within the scope of **Formula 6**, and  
12 **Compound A33b** is within the scope of **Formula 3**.



Reaction Scheme 6



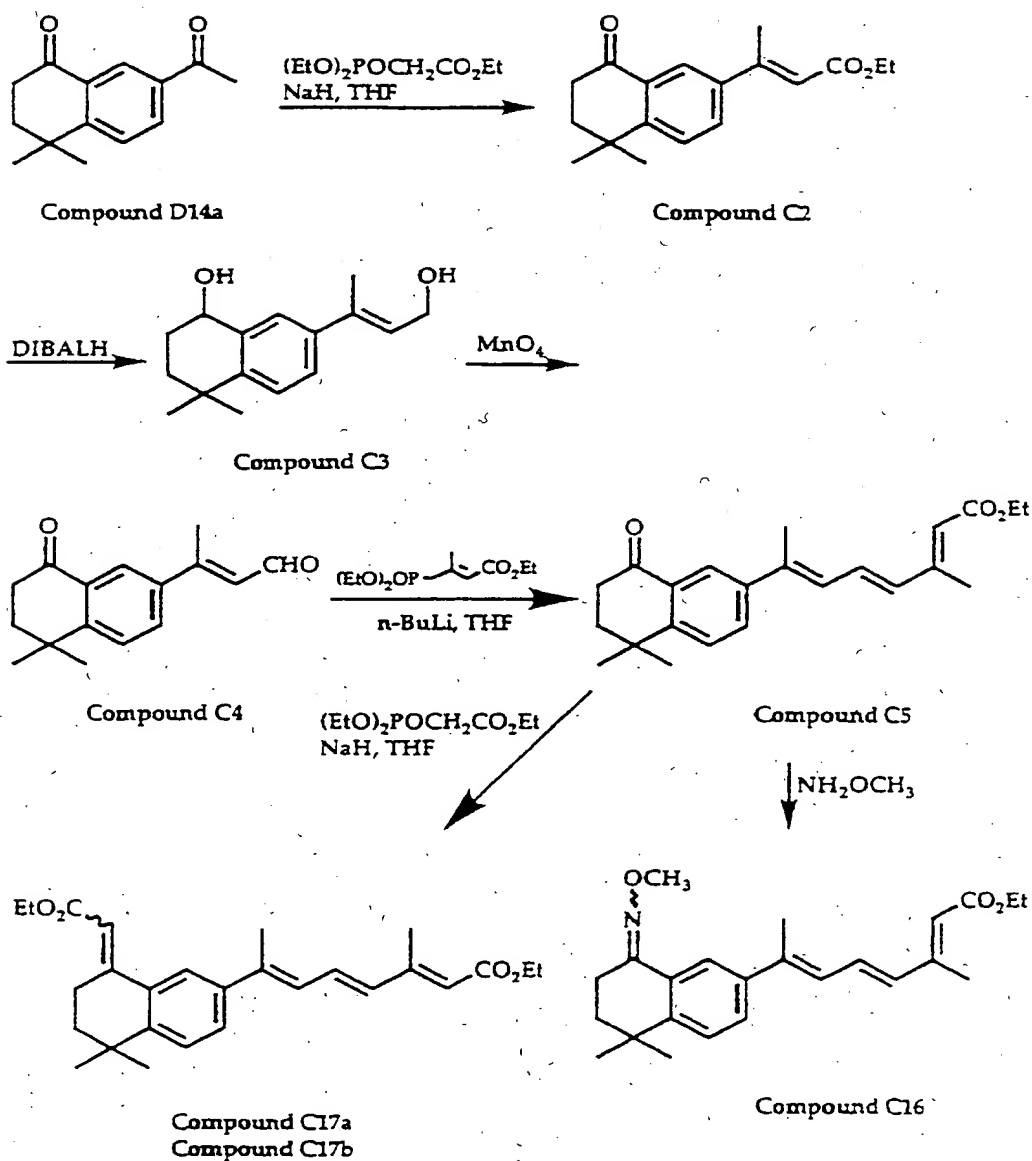
Reaction Scheme 6 (continued)

1           **Reaction Scheme 6** provides examples for the synthesis of  
2 compounds of the invention where in accordance with **Formulas 1 - 6**  
3 the **Z** group is  $-(CR_1=CR_1)_n-$  and  $n'$  is 0; in other words where there is  
4 no linking group between the tetrahydronaphthalene or  
5 dihydronaphthalene nucleus and the  $Y(R_2)$ -**A-B** group. For the  
6 synthesis of these examples the starting material is  
7 6-bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (**Compound F**)  
8 which is reacted with *n*-butyl lithium and triisopropylborate in an aprotic  
9 solvent such as toluene to give after hydrolysis (5,6,7,8-tetrahydro-5,5-  
10 dimethylnaphth-2-yl)boronic acid (**Compound B13**). **Compound B13**  
11 and related boronic acid derivatives (such as **Compound B14** in this  
12 scheme) are suitable for coupling with a reagent having the formula  $X_3$ -  
13  $Y(R_2)$ -**A-B** where  $X_3$  is halogen, and the remaining symbols are defined  
14 as for **Formulas 1 - 6**. **Reaction Scheme 6** illustrates this coupling  
15 reaction with ethyl 6-bromo-naphthalene-2-carboxylate in the presence  
16 of tetrakis-triphenyl-phosphine palladium(0) to yield ethyl-6-[5,6,7,8-  
17 tetrahydro-5,5-dimethyl-naphth-2-yl]naphthoate (**Compound B1**).  
18 **Compound B1** of the invention is within the scope of **Formula 2**. Other  
19 reagents corresponding to formula  $X_3$ - $Y(R_2)$ -**A-B** are readily available in  
20 accordance with the chemical literature and/or can be obtained in  
21 accordance with state-of-the-art synthetic methodology. Examples for  
22 such other reagents are ethyl 4-bromobenzoate and ethyl 2-  
23 bromopyridine-5-carboxylate.

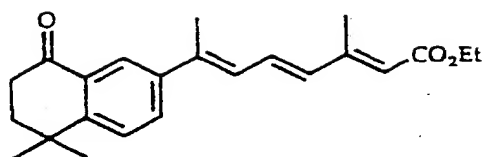
24           Continuing on with the description of **Reaction Scheme 6**, 6-  
25 bromo-1,2,3,4-tetrahydro-1,1-dimethyl-4-hydroxynaphthalene is reacted  
26 in the presence of base with *t*-butyldimethylsilyl chloride to provide 6-  
27 bromo-1,2,3,4-tetrahydro-1,1-dimethyl-4-(*t*-  
28 butyldimethylsilyloxy)naphthalene (**Compound B15**). The starting 6-  
29 bromo-1,2,3,4-tetrahydro-1,1-dimethyl-4-hydroxynaphthalene can be  
30 obtained by reduction of  
31 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**).

1 Under conditions similar to the ones described above **Compound B15** is  
2 converted to the boronic acid derivative (5,5-dimethyl-8-(*t*-  
3 butyldimethylsilyloxy)-5,6,7,8-tetrahydro-naphth-2-yl)boronic acid  
4 (**Compound B14**). **Compound B14** is then coupled with ethyl 6-bromo-  
5 naphthalene-2-carboxylate to yield ethyl 6-[5,6,7,8-tetrahydro-5,5-  
6 dimethyl-8-(*t*-butyldimethylsilyloxy)-naphth-2-yl]naphth-2-oate  
7 (**Compound B3**). **Compound B3** is then reacted with  
8 tetrabutylammonium fluoride to remove the *t*-butyldimethylsilyl blocking  
9 group and to give ethyl 6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-  
10 naphth-2-yl]naphth-2-oate (**Compound B4**). **Compound B4** can be  
11 acylated to give ethyl 6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(*O*-acetyl)-  
12 naphth-2-yl]naphth-2-oate (**Compound B10**), or methoxymethylated with  
13 methoxymethyl chloride in the presence of base (preferably ethyl *N,N*-  
14 diisopropylamine, *Hunig's* base) to give ethyl 6-[5,6,7,8-tetrahydro-5,5-  
15 dimethyl-8-(methoxymethyloxy)-naphth-2-yl]naphth-2-oate (**Compound**  
16 **B8**), and oxidized with *N*-methyl morpholine *N*-oxide to provide ethyl -  
17 6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-one-2-yl]-naphthalen-2-  
18 oate (**Compound B6**). **Compounds B8** and **B10** of the invention are  
19 within the scope of **Formula 1**, whereas **Compound B6** is within the  
20 scope of **Formula 2**. **Compound B6** can be converted into the *O*-  
21 methyloxime (ethyl 6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-*anti*-  
22 (*O*-methyl-oxime)-2-yl]-naphthalen-2-oate (**Compound B11**) not shown  
23 in the scheme) and into other derivatives such as oximes, imines,  
24 hydrazones and the like, as is described above in connection with  
25 **Reaction Scheme 2**. Further derivatives of **Compound B6** (and of  
26 analogous compounds) wherein the 8-oxo function of the molecule is  
27 modified can be obtained in accordance with the general synthetic  
28 methodology described in this specification. For example the  
29 trifluoromethylsulfonyl (triflate) derivative can be obtained in analogy to  
30 the reaction leading to **Compound A9** as described in **Reaction Scheme**  
31 **2**, and the trifluoromethylsulfonyl (triflate) derivative is reacted with

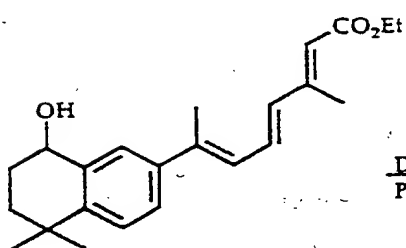
the reagents  $R_{14}Me$  to provide compounds of Formula 6.



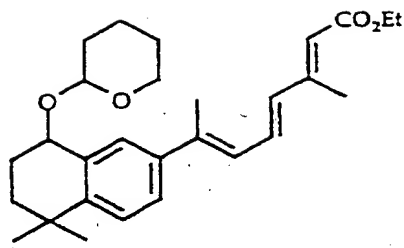
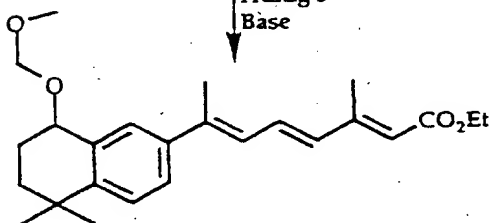
Reaction Scheme 7



Compound C5



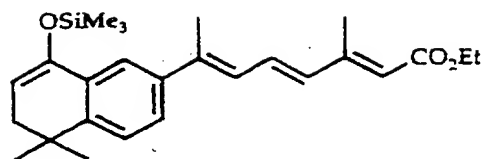
Compound C13

Compound C29a  
Compound C29b

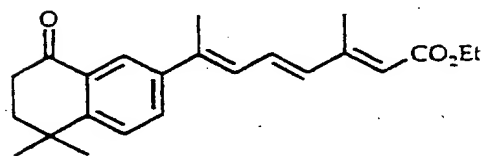
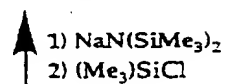
Compound C26

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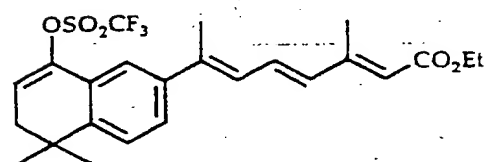
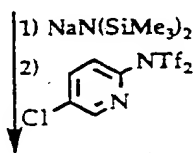
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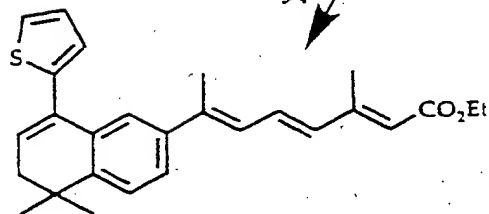
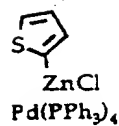
Compound C28



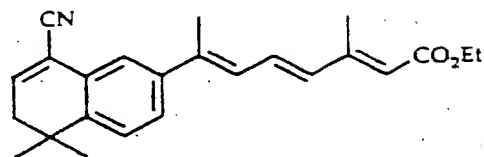
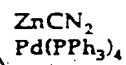
Compound C5



Compound C14



Compound C15



Compound C21

Reaction Scheme 7 (end)

1     **Reaction Scheme 7** discloses a preferred example of a synthetic  
2     route leading to compounds of the invention where with reference to  
3     **Formulas 1 - 6** the symbol **Z** represents  $-(CR_1=CR_1)_{n'}$ , where  $n'$  is 3,  
4     and there is no  $Y(R_2)$  group. Thus, 4,4-dimethyl-7-acetyl-1,2,3,4-  
5     tetrahydronaphthalen-1(2H)-one (**Compound D14a**) is reacted in a  
6     *Horner Emmons* type reaction with triethylphosphonoacetate in the  
7     presence of sodium hydride in an ether type solvent such as  
8     tetrahydrofuran. Conditions of the *Horner Emmons* reaction are well  
9     known in the art, and it is also well known that usually a related *Wittig*  
10    type reaction can also be employed using a trialkylphosphonium reagent  
11    instead of the phosphonate reagent, to yield the same products as is  
12    obtained in the *Horner Emmons* reaction. The product of the *Horner*  
13    *Emmons* reaction in this example is ethyl 3-[4,4-dimethyl-1,2,3,4-  
14    tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-enoate (**Compound C2**)  
15    which is reduced with diisobutyl aluminum hydride to provide 3-[1-  
16    hydroxy-4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-7-yl]but-2(E)-en-1-ol  
17    (**Compound C3**). **Compound C3** is oxidized back to the aldehyde and  
18    ketone "stage" with manganese dioxide to give 3-[4,4-dimethyl-1,2,3,4-  
19    tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-en-al (**Compound C4**).  
20    **Compound C4** is subjected to yet another *Horner Emmons* type reaction  
21    with diethyl-(E)-3-ethoxycarbonyl-2-methylallylphosphonate (available  
22    from the chemical literature; see: *Vuligunda et al.* Biorganic Medical  
23    Chemistry Letters, (1996) 6 p213-218) in tetrahydrofuran in the  
24    presence of *n*-butyl lithium, to yield ethyl 7-[4,4-dimethyl-3,4-  
25    dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
26    6(E)trienoate (**Compound C5**).

27     **Compound C5** of the invention is within the scope of **Formula 2**, and  
28     is also readily converted to further compounds of the invention in  
29     accordance with the generic principles disclosed in this specification.  
30     Several examples of reactions which provide further compounds of the  
31     invention using **Compound C5** as the starting material are shown in

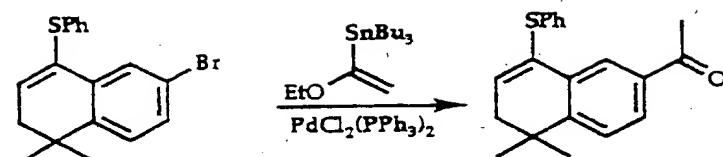


1     **Reaction Scheme 7.** These reactions are described in less detail to the  
2     extent that they are of the types which have been described above. Thus,  
3     the "oxo" compound ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-  
4     1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound**  
5     **C5**) is saponified to yield the free acid (not shown in the scheme), is  
6     converted to the *O*-methyl-oxime derivative (**Compound C16**); to ethyl  
7     7-[4,4-dimethyl-3,4-dihydro-1-(trimethylsiloxy)-naphth-7-yl]3,7-dimethyl-  
8     hepta-2(E),4(E),6(E)-trienoate (1-trimethylsilyloxy derivative  
9     **Compound C28**); and to ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1-  
10    trifluoromethylsulfonyloxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
11    6(E)trienoate ("triflate", **Compound C14**). **Compounds C14 and C28**  
12    are within the scope of **Formula 5**, whereas **Compound C16** is within  
13    the scope of **Formula 4**. Another *Horner Emmons* type reaction of  
14    **Compound C5** which leads to compounds within the scope of **Formula 3**  
15    (**Compounds 17a and 17B**) is shown in the scheme.

16       In the examples shown in **Reaction Scheme 7** the "oxo" compound  
17    ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]-3,7-  
18    dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound C5**) is also  
19    reduced with  $\text{ZnBH}_4$  to yield the corresponding secondary alcohol,  
20    ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-  
21    dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound C13**). **Compound**  
22    **C13** is reacted with chloromethylmethyl ether to give (-/+ )ethyl 7-[4,4-  
23    dimethyl-1,2,3,4-tetrahydro-1-(*O*-methoxymethyl)-naphth-7-yl]3,7-  
24    dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound C26**); alternatively  
25    it is reacted with 3,4-dihydro-2H-pyran in methylene chloride in the  
26    presence of *p*-toluene sulfonic acid (*p*-TsOH) to give the diastereomeric  
27    dihydropyranoxy derivatives, (+/-)ethyl 7-[4,4-dimethyl-1,2,3,4-  
28    tetrahydro-1(RS)-(2'(RS)-  
29    tetrahydropyranoxy)-naphth-2-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-  
30    trienoate (**Compound C29a**) and (+/-)ethyl 7-[4,4-dimethyl-1,2,3,4-  
31    tetrahydro-1(RS)-(2'(SR)-tetrahydropyranoxy)-naphth-2-yl]-3,7-dimethyl-

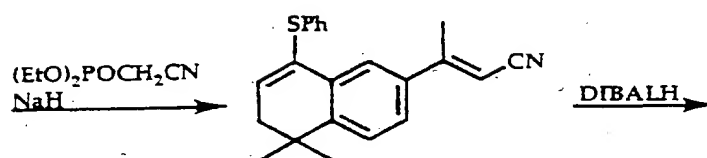
1 hepta-2(E),4(E),6(E)-trienoate (**Compound C29b**). **Compounds C13**,  
2 **C26**, **C29a** and **C29b** of the invention are within the scope of **Formula**  
3 **1**.

4 The trifluoromethylsulfonate (triflate) derivative **Compound C14** is  
5 itself an important starting material for the syntheses of several  
6 compounds of the invention within the scope of **Formula 6**; among  
7 these the preparations of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1-  
8 (2-thienyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound**  
9 **C15**) and of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1-cyano-7-yl]-  
10 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound 21**) are  
11 illustrated in the reaction scheme.

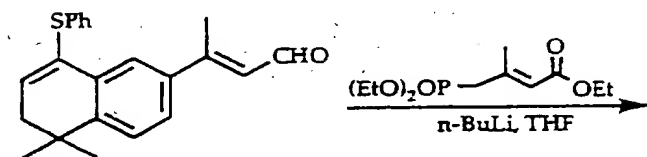


Compound A35

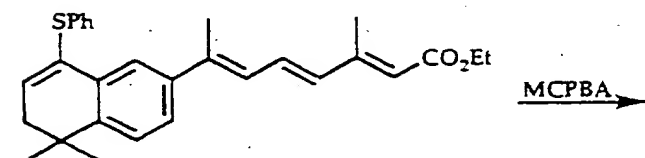
Compound C7



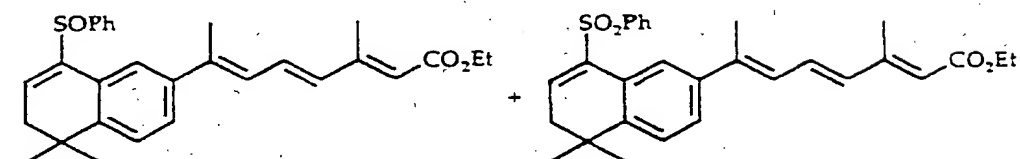
Compound C8



Compound C9



Compound C10



Compound C11a

Compound C11b

Reaction Scheme 8

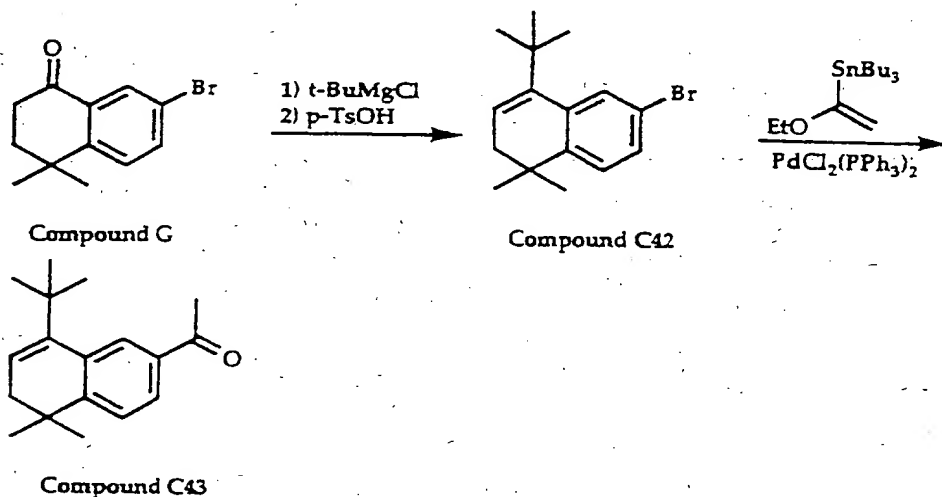
1       **Reaction Scheme 8** discloses other examples for synthesizing  
2 preferred compounds of the invention where with reference to **Formula**  
3 **5** the symbol **Z** represents  $-(CR_1=CR_1)_{n'}$ , where  $n'$  is 3, and there is no  
4 **Y(R<sub>2</sub>)** group. The starting compound for the series of reactions shown  
5 in this scheme is 4,4-dimethyl-7-bromo-1-phenylthio-3,4-  
6 dihydronaphthalene (**Compound A35**) which can be obtained as shown  
7 in **Reaction Scheme 3**. Thus, referring now to **Reaction Scheme 8**,  
8 **Compound A35** is reacted with 1-ethoxyvinyltributyltin (EVTB, available  
9 from Aldrich Chemical Co.) in the presence of  
10 bis(triphenylphosphine)palladium(II)chloride in tetrahydrofuran to  
11 provide, after acid work-up, 4,4-dimethyl-7-acetyl-1-phenylthio-3,4-  
12 dihydronaphthalene (**Compound C7**). **Compound C7** is subjected to a  
13 *Horner Emmons* reaction (as described above) with  
14 diethylcyanomethylphosphonate (available from Aldrich Chemical Co.)  
15 to provide 3-[4,4-dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-  
16 2-en(E)-nitrile (**Compound C8**). **Compound C8** is reduced with  
17 diisobutyl aluminium hydride to provide the corresponding aldehyde, 3-  
18 [4,4-dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-2-en(E)-  
19 aldehyde (**Compound C9**). **Compound C9** is subjected to still another  
20 *Horner Emmons* reaction with the reagent diethyl-(E)-3-ethoxycarbonyl-  
21 2-methylallylphosphonate to yield ethyl 7-[4,4-dimethyl-1-phenylthio-  
22 3,4,-dihydronaphthalen-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate  
23 (**Compound C10**). **Compound C10** of the invention is within the scope  
24 of **Formula 5**.

25       In other preferred examples not shown in the schemes but described  
26 in the Specific Examples, a sequence of reaction which is analogous to  
27 the above-described reactions of **Reaction Scheme 8** is conducted,  
28 starting with 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
29 dimethylnaphthalene (**Compound A37**), or with 7-bromo-1(2H)-  
30 (phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphthalene (**Compound**  
31 **C37**) to provide further examples for compounds of the invention, such

as ethyl-7-[1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethyl-naphthalen-7-yl]-3,7-dimethyl-hept-2(E),4(E),6(E)-trienoate (**Compound C36**) and ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-phenylbenzylidenyl]-naphth-7-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound C41**).

**Compounds C36 and C41** of the invention are within the scope of **Formula 3**.

**Compound C10** is converted by oxidation with *meta*-chloroperoxybenzoic acid to the corresponding sulfone and sulfoxide, ethyl 7-[4,4-dimethyl-1-phenylsulfonyl-3,4-dihydronaphthalen-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound C11a**) and ethyl 7-[4,4-dimethyl-1-phenylsulfoxide-3,4-dihydronaphthalen-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound C11b**), which are also within the scope of **Formula 5**.

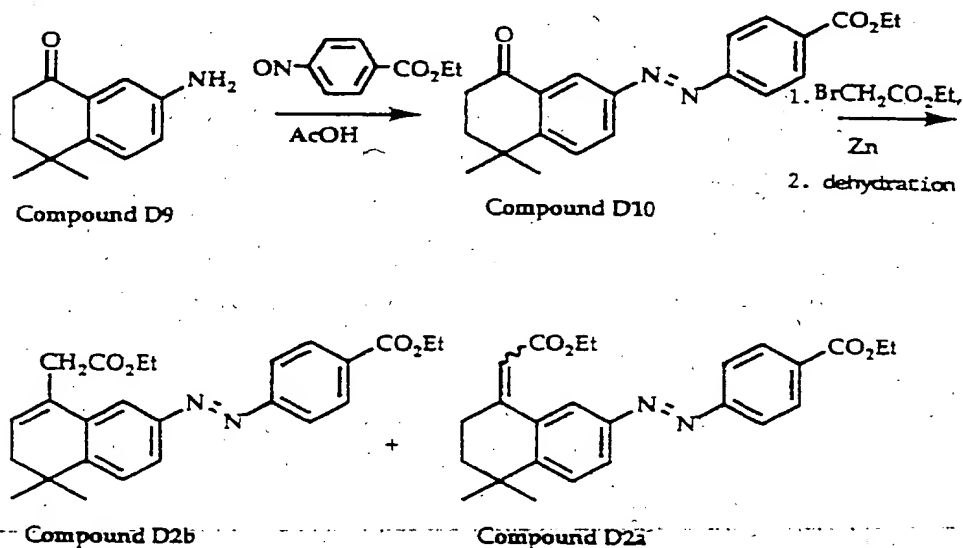


#### Reaction Scheme 9

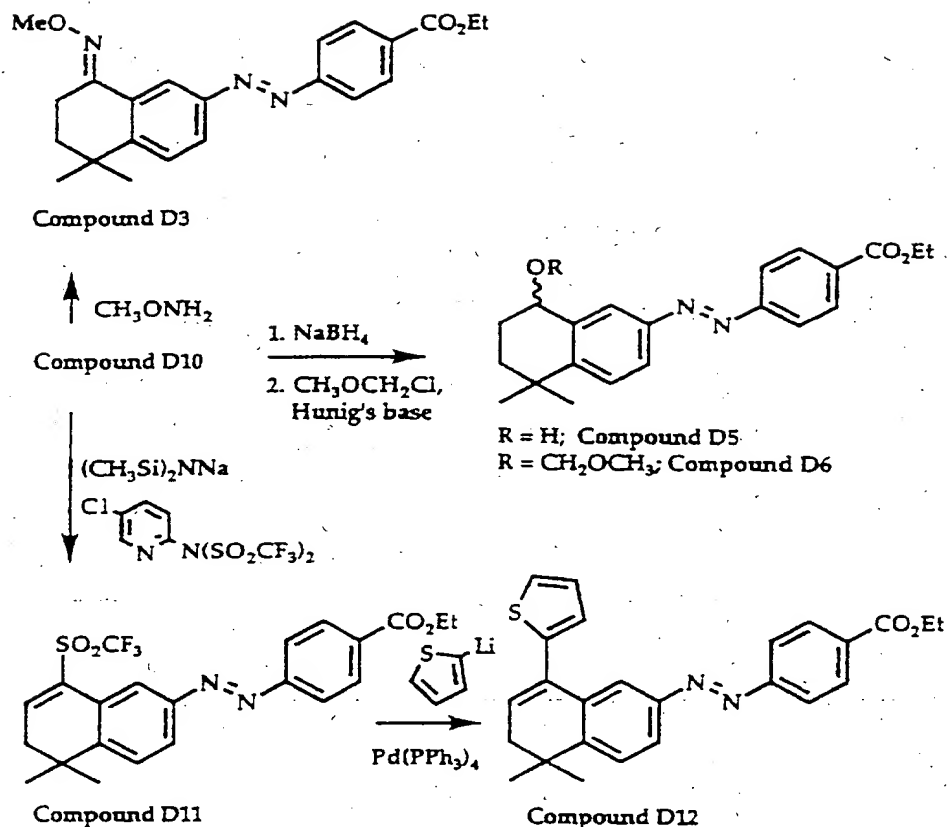
**Reaction Scheme 9** discloses the preferred method of synthesis of a starting material from which certain examples for compounds of the invention within the scope of **Formula 6** are preferably made. In accordance with this scheme

7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**)

is reacted with *t*-butylmagnesium chloride in tetrahydrofuran in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(H)-pyrimidinone (DMPU). Thereafter, the resulting intermediate tertiary alcohol is heated in the presence of acid (*p*-toluenesulfonic acid) to give 7-bromo-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene (**Compound C42**). **Compound C42** is reacted with 1-ethoxyvinyltributyltin (EVTB) in the presence of Pd(0) catalyst to yield after acidic work-up 7-acetyl-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene (**Compound C43**). **Compound C43** is subjected to a sequence of reactions of the type described above in connection with Reaction Scheme 8, starting with a *Horner Emmons* reaction with diethyl cyanomethylphosphonate, to eventually provide ethyl 7-[4,4-dimethyl-3,4-dihydro-1-(1,1-dimethylethyl)-naphth-7-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound C46**). **Compound C46** of the invention is within the scope of Formula 6.



Reaction Scheme 10



### Reaction Scheme 10 (continued)

Reaction Scheme 10 discloses a preferred synthetic route to certain exemplary compounds of the invention where, with reference to Formulas 1 - 6 the Z group is  $-\text{N}=\text{N}-$  (azo) moiety. For the examples shown in this scheme the starting compound is 3,4-dihydro-4,4-dimethyl-7-amino-naphthalen-1(2H)-one (Compound D9). Compound D9 is coupled with a nitroso compound of the formula  $\text{ON}-\text{Y}(\text{R}_2)-\text{A}-\text{B}$ , which in the herein shown example is ethyl 4-nitrosobenzoate (available in accordance with the chemical literature; see *Kagechika et al. J. Med.*

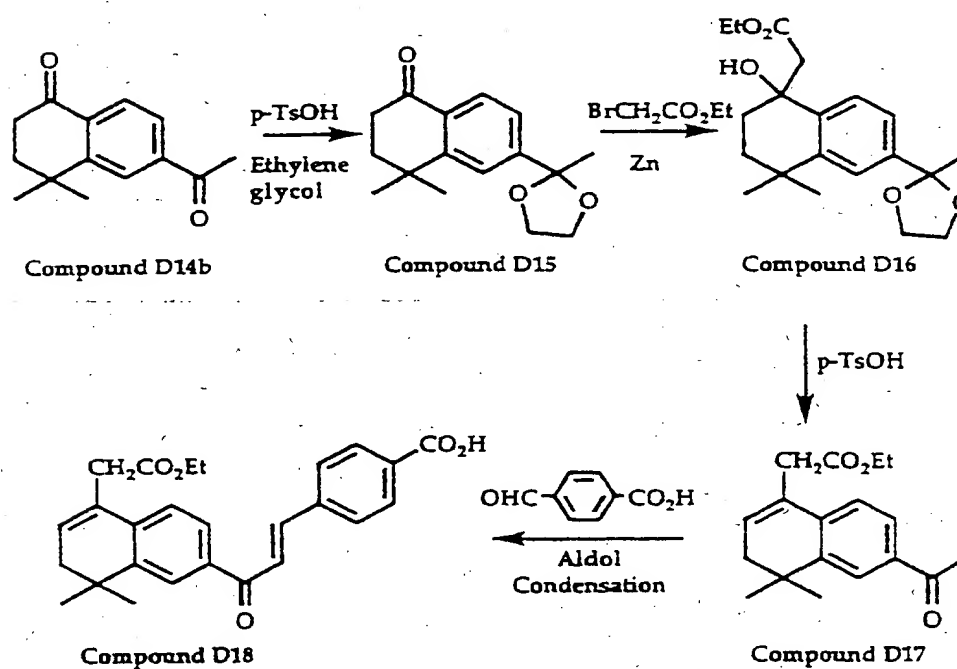
1 Chem. (1989) 32, 1098-1108). The coupling reaction is conducted in  
2 glacial acetic acid and yields ethyl 4-[(5,6-dihydro-5,5-dimethyl-8(7H)-  
3 one-naphthalen-2-yl)azo]-benzoate (**Compound D10**). **Compound D10**  
4 of the invention is within the scope of **Formula 2**. **Compound D10** is  
5 reacted in a *Reformatsky* reaction with ethyl bromoacetate to provide  
6 (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-8-carbethoxymethyl-5,6,7,8-  
7 tetrahydronaphth-2-yl)azo]benzoate (**Compound D1**). **Compound D1** of  
8 the invention is within the scope of **Formula 1**. Dehydration of  
9 **Compound D1** with dicyclohexylcarbodiimide and cuprous chloride in  
10 benzene provides the isomeric compounds ethyl 4-[(5,5-dimethyl-8(7H)-  
11 (carbethoxymethylidenyl)-5,6-dihydronaphthalen-2-yl)azo]benzoate  
12 (**Compound D2a**) and ethyl 4-[(5,5-dimethyl-8-(carbethoxymethyl)-5,6-  
13 dihydronaphthalen-2-yl)azo]benzoate (**Compound D2b**). **Compound**  
14 **D2a** of the invention is within the scope of **Formula 3**, and **Compound**  
15 **D2b** is within the scope of **Formula 6**.

16 The "oxo" compound ethyl 4-[(5,6-dihydro-5,5-dimethyl-8(7H)-one-  
17 naphthalen-2-yl)azo]-benzoate (**Compound D10**) serves as starting  
18 material for reactions which lead to further compounds of the invention  
19 in accordance with synthetic methodology that has been described  
20 above. More particularly, in the examples shown in **Reaction Scheme**  
21 **10** **Compound D10** is converted into the *O*-methyl oxime derivative ethyl  
22 4-[(8(7H)-*anti*-(*O*-methyl oxime)-5,5-dimethyl-5,6-dihydronaphthalen-2-  
23 yl)azo]benzoate (**Compound D3**), into the "triflate" ethyl 4-[(5,6-  
24 dihydro-5,5-dimethyl-8-(trifluoromethylsulfonyl)oxy-naphthalen-2-yl)azo]-  
25 benzoate (**Compound D11**) and is reduced to the secondary alcohol (+/-  
26 ) ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-  
27 yl)azo]benzoate (**Compound D5**). The *O*-methyl oxime derivative  
28 (**Compound D3**) of the invention is within the scope of **Formula 4**, the  
29 "triflate" **Compound D11** is in the scope of **Formula 5**, whereas the  
30 secondary alcohol **Compound D5** is within the scope of **Formula 1**.

31 The secondary alcohol, **Compound D5** is further converted into the



methoxymethyl derivative (+/-) ethyl 4-[(5,5-dimethyl-8-(methoxymethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)azo]benzoate (Compound D6) within the scope of Formula 1, and the "triflate" is reacted with thienyl lithium in the presence of  $\text{ZnCl}_2$  and  $\text{Pd}(0)$  catalyst to provide ethyl 4-[(5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-yl)azo]benzoate (Compound D12).



Reaction Scheme 11

1 Referring now to **Reaction Scheme 11** a preferred example for the  
2 synthesis of those compounds of the invention is described where, with  
3 reference to **Formulas 1 - 6** the Z group is  $-\text{CO}-\text{CR}_1=\text{CR}_1-$ . As it will  
4 become apparent from the reaction scheme, these compounds are  
5 obtained as a result of an aldol condensation between an appropriately  
6 substituted tetrahydro or dihydronaphthalene ketone derivative and an  
7 aldehyde of the formula  $\text{OCH}-\text{Y}(\text{R}_2)\text{A}-\text{B}$ . In the example shown in  
8 **Reaction Scheme 11** the exocyclic ketone function of 3,4-dihydro-4,4-  
9 dimethyl-6-acetyl-naphthalen-1(2H)-one (**Compound D14b**) is reacted  
10 with ethylene glycol and acid to provide 6-(2-methyl-1,3-dioxolan-2-yl)-  
11 3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound D15**) where  
12 one ketone function is protected. **Compound D15** is then reacted with  
13 ethyl bromoacetate in a *Reformatsky* reaction to give (+/-) 6-(2-methyl-  
14 1,3-dioxolan-2-yl)]-1,2,3,4-tetrahydro-4,4-dimethyl-1-hydroxy-1-  
15 (carboethoxymethyl)-naphthlene (**Compound D16**). Treatment with acid  
16 of **Compound D16** removes the 1,3-dioxolanyl protecting group and also  
17 introduces a double bond into the tetrahydronaphthalene nucleus, thus  
18 providing 3,4-dihydro-4,4-dimethyl-1-(carbethoxymethyl)-6-acetyl-  
19 naphthalene (**Compound D17**).

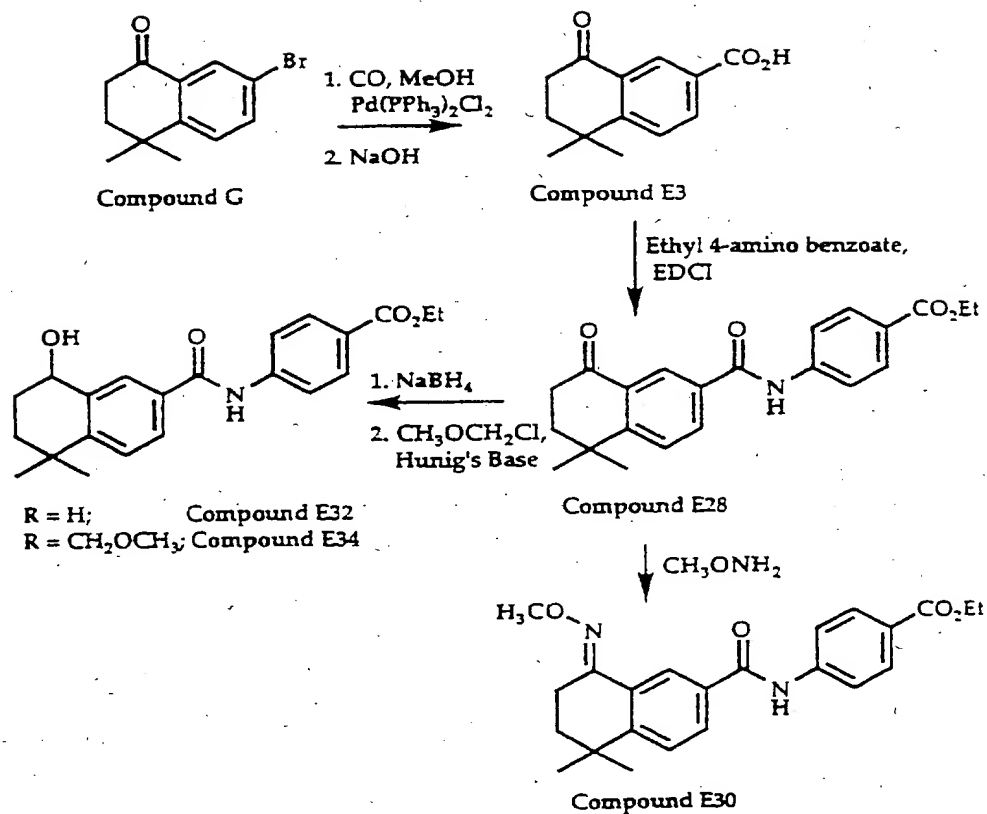
20 An alternate method for obtaining dihydronaphthalene compounds  
21 having the 6-acetyl substituent and a substituent in the 1-position  
22 (attached to the vinylic carbon) is to react **Compound D15** with sodium  
23 bis(trimethylsilyl)amide and 2-[N,N-bis(trifluorometh-  
24 ylsulfonyl)amino]-5-chloropyridine in an inert ether type solvent, such as  
25 tetrahydrofuran, at low temperatures ( $-78^\circ\text{C}$  and  $0^\circ\text{C}$ ). As noted above  
26 in connection with an analogous "triflate" forming reaction, this reaction  
27 proceeds through a sodium salt intermediate which is usually not  
28 isolated. The overall reaction results in a trifluoromethylsulfonyloxy  
29 derivative, which is thereafter reacted with an organometal derivative,  
30 again in analogy to the preceding description of synthesizing compounds  
31 of **Formula 6** from the "triflate" derivatives.

Returning now to the description of **Reaction Scheme 11**, **Compound D17** is reacted with 4-carboxybenzaldehyde in an aldol condensation reaction to give ethyl (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-(carbethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-one]benzoate (**Compound D18**). The just described aldol condensation reaction is conducted in the presence of base in an alcoholic solvent. Preferably, the reaction is conducted in methanol or ethanol in the presence of sodium hydroxide. Those skilled in the art will recognize the aldol condensation reaction of this example as a Claisen-Schmidt reaction. (See March: Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, pp 694 695 McGraw Hill (1968). Examples of other reagents analogous to 4-carboxybenzaldehyde and suitable for the condensation reaction to introduce heterocyclic Y(R<sub>2</sub>) groups into the compounds of the present invention 1) are: 5-carboxypyridine-2-carboxaldehyde, 4-carboxypyridine-2-carboxaldehyde, 4-carboxythiophene-2-carboxaldehyde, 5-carboxythiophene-2-carboxaldehyde, 4-carboxyfuran-2-carboxaldehyde, 5-carboxyfuran-2-carboxaldehyde, 4-carboxyacetophenone, 2-acetylpyridine-5-carboxylic acid, 2-acetylpyridine-4-carboxylic acid, 2-acetylthiophene-4-carboxylic acid, 2-acetylthiophene-5-carboxylic acid, 2-acetylfuran-4-carboxylic acid, and 2-acetylfuran-5-carboxylic acid. The latter compounds are available in accordance with the chemical literature; see for example Decroix et al., *J. Chem. Res.(S)*, 1978, 4, 134; Dawson et al., *J. Med. Chem.*, 1983, 29, 1282; and Queguiner et al., *Bull Soc. Chimique de France*, 1969, No. 10, pp 3678-3683. **Compound D18** of the invention is within the scope of **Formula 6**.

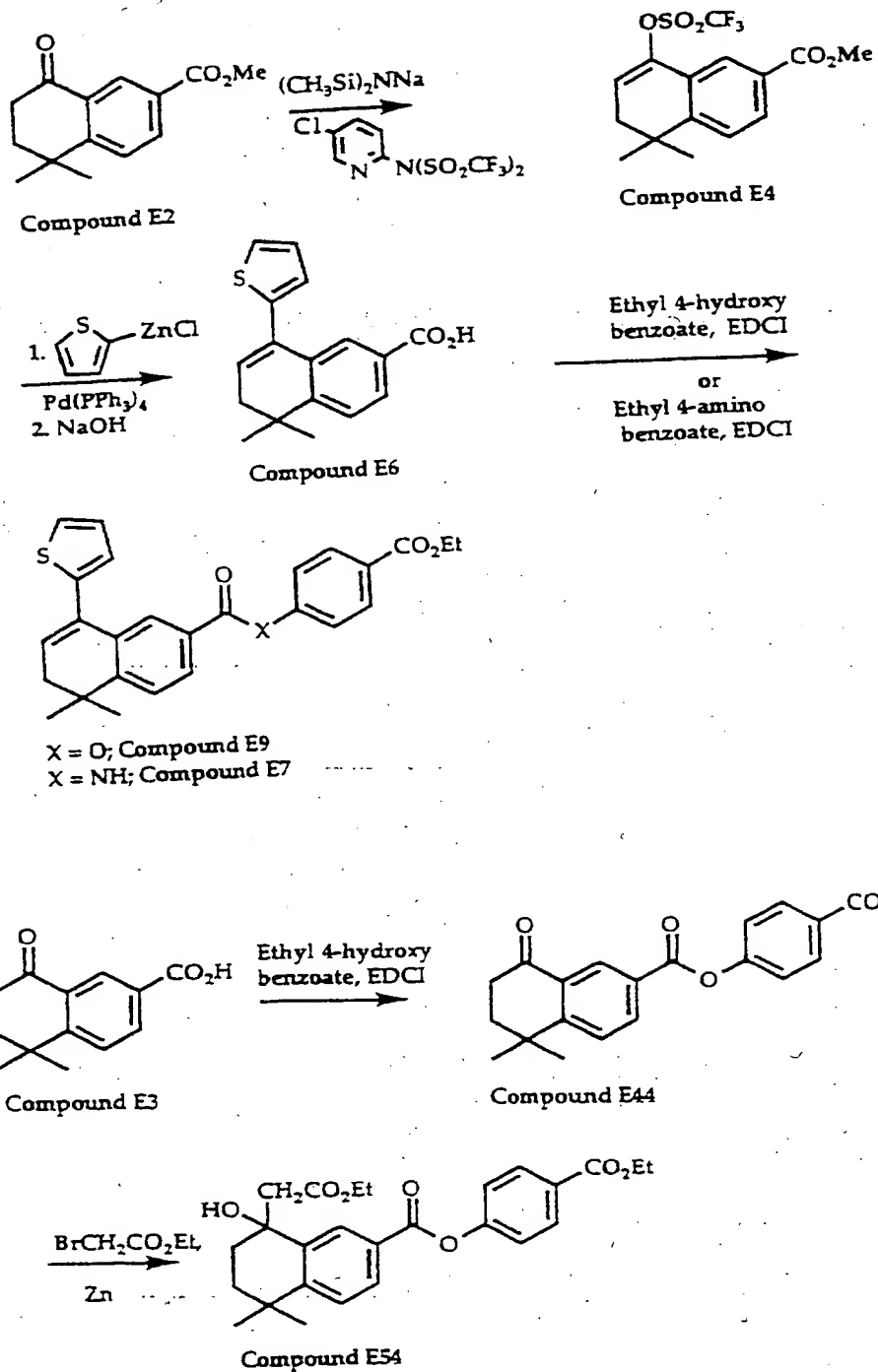
To obtain further preferred examples of the compounds of the invention where the Z group is -CO-CR<sub>1</sub>=CR<sub>1</sub>-, the aldol condensation reaction shown in **Reaction Scheme 11** is performed on the following compounds:

3,4-dihydro-4,4-dimethyl-6-acetyl-1-(1,1-dimethylethyl)naphthalene

- 1 (Compound D19);  
2 6-Acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
3 (Compound D22);  
4 (+/-) 1-(methoxymethyloxy)-6-acetyl-1,2,3,4-tetrahydro-4,4-dimethyl-  
5 naphthalene (Compound D26); and  
6 6-Acetyl-1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
7 dimethylnaphthalene (Compound D28)  
8 to provide respectively the following examples of compounds of the  
9 invention:  
10 (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-(1,1-dimethyl-ethyl)naphth-6-yl)-  
11 prop-1-en-3-one]benzoic acid (Compound D20, Formula 6);  
12 (E)-4[3-{1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalen-  
13 6-yl}-prop-1-en-3-one]benzoic acid (Compound D23, Formula 3);  
14 (E)-4-[3-(1,2,3,4-tetrahydro-4,4-dimethyl-1-(methoxymethyloxy)-  
15 naphthalen-6-yl)-prop-1-en-3-one]benzoic acid (Compound D27,  
16 Formula 1), and  
17 (E)-4[3-{1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
18 dimethylnaphthalen-6-yl}-prop-1-en-3-one]benzoic acid (Compound  
19 D29, Formula 4).



Reaction Scheme 12



Reaction Scheme 12 (continued)

1        **Reaction Scheme 12** discloses the presently preferred methods for  
2 synthesizing preferred examples of compounds of the invention where  
3 with reference to **Formulas 1 - 6** the Z group is -COO- or -CONH-. As  
4 is shown in the scheme,  
5 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**)  
6 is reacted with carbon monoxide in the presence of palladium(II)-  
7 bis(triphenylphosphine)chloride, 1,3-bis(diphenylphosphino)-propane,  
8 DMSO, methanol and triethylamine to obtain the corresponding  
9 carboxylic acid methyl ester, methyl 5,5-dimethyl-5,6-dihydro-  
10 naphthalen-8(7H)-one-2-carboxylate (**Compound E2**), which is thereafter  
11 saponified to provide 5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-  
12 carboxylic acid (**Compound E3**). **Compound E3** is a free carboxylic acid  
13 which is reacted either with compounds of the formula  $H_2N-Y(R_2)-A-B$   
14 to provide compounds of the invention where Z is -CONH-, or with  
15 compounds of the formula  $HO-Y(R_2)-A-B$  to provide compounds of the  
16 invention where Z is -COO-. Those skilled in the art will recognize  
17 that these compounds of the invention are amide and ester compounds,  
18 respectively. Generally speaking several known methods for amide and  
19 ester formation may be employed for their synthesis from **Compound E3**  
20 or analogous carboxylic acid compounds. For example, **Compound E3**  
21 or analogous carboxylic acid compounds can be converted into the acid  
22 chloride by known methods and thereafter reacted with the amines or  
23 esters of formula  $H_2N-Y(R_2)-A-B$  or formula  $HO-Y(R_2)-A-B$   
24 respectively. The presently preferred method for synthesis, however  
25 utilizes the reagents 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
26 hydrochloride (EDCI) and 4-N,N-dimethylaminopyridine in an aprotic  
27 solvent for the amide or ester formation. Those skilled in the art will  
28 also recognize that the compounds of formula  $H_2N-Y(R_2)-A-B$  and  
29 formula  $HO-Y(R_2)-A-B$  are aromatic or heteroaromatic amines or  
30 hydroxyl derivatives, which can be obtained in accordance with the  
31 state-of-the-art.

1 Referring now back to **Reaction Scheme 12** that describes certain  
2 preferred specific examples, 5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-  
3 one-2-carboxylic acid (**Compound E3**) is reacted in the presence of 1-(3-  
4 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 4-  
5 (dimethylamino)pyridine in methylene chloride to give ethyl 4-[(5,5-  
6 dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-yl)carboxamido]benzoate  
7 (**Compound 28**). **Compound 28** of the invention is in the scope of  
8 **Formula 2**. **Reaction Scheme 12** discloses its conversion by reactions of  
9 the type described above, to ethyl 4-[(5,5-dimethyl-8(7H)-*anti*-(O-  
10 methyloxime)-5,6-dihydronaphthalen-2-yl)carboxamido]benzoate  
11 (**Compound E30**, **Formula 4**) and (+/-) 4-[(5,5-dimethyl-8-hydroxy-  
12 5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoic acid (**Compound**  
13 **E32**, **Formula 1**). **Compound E32** is converted to the methoxymethyl  
14 derivative (+/-) ethyl 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
15 tetrahydronaphthalen-2-yl)carboxamido]benzoate (**Compound E34**)  
16 within the scope of **Formula 1**. Each of these amide compounds can  
17 have their respective COOEt group saponified to provide the free  
18 carboxylic acid or its salt.

19 Referring still to **Reaction Scheme 12**, methyl 5,5-dimethyl-5,6-  
20 dihydro-naphthalen-8(7H)-one-2-carboxylate (**Compound E2**) is  
21 converted, under conditions described above for analogous reactions,  
22 into the trifluoromethylsulfonyl ("triflate") derivative, methyl 5,5-  
23 dimethyl-5,6-dihydro-8-(trifluoromethylsulfonyl)oxy-naphthalene-2-  
24 carboxylate (**Compound E4**). **Compound E4** serves as an important  
25 intermediate for the synthesis of compounds within the scope of  
26 **Formula 6**. In the preferred examples shown in the reaction scheme,  
27 **Compound E4** is reacted with the lithium derivative of thiophene in the  
28 presence of  $\text{ZnCl}_2$  and Pd(0) catalyst to provide the thienyl substituted  
29 carboxylic acid methyl ester, (**Compound E5**). The latter compound is  
30 saponified to give 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalene-2-  
31 carboxylic acid (**Compound E6**). **Compound E6** is coupled with ethyl 4-



1 aminobenzoate to give ethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
2 naphthalen-2-yl)carboxamido]-benzoate (**Compound E7**), and with ethyl  
3 4-hydroxybenzoate to provide ethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-  
4 thienyl)-naphthalen-2-yl)carbonyl]oxy]-benzoate (**Compound E9**).

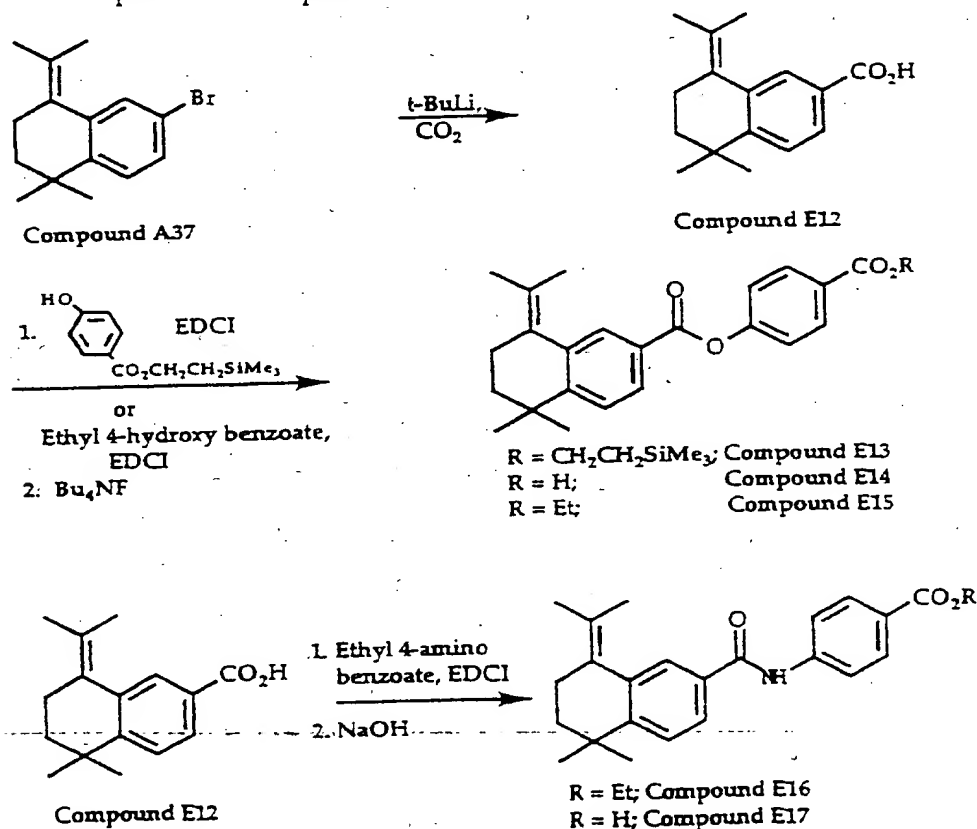
5 **Compounds E7 and E9** of the invention are within the scope of  
6 **Formula 6**.

7 As it will be readily recognized in the art, the free carboxylic acid  
8 derivatives of the invention could not be obtained (or could be obtained  
9 only with difficulty) from the carbonyloxy compounds of the present  
10 invention by a process of saponification of the ester compounds such as  
11 **Compound E9**. However, the above-mentioned free carboxylic acids,  
12 such as 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
13 yl)carbonyl]oxy]-benzoic acid (**Compound E11**) can be obtained from  
14 the corresponding 2-(trimethylsilyl)ethyl esters (such as 2-  
15 (trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
16 naphthalen-2-yl)carbonyl]oxy]-benzoate, (**Compound E10**) by treatment  
17 with tetrabutylammonium fluoride. **Compound E10** and like compounds  
18 can be obtained by coupling reactions of the type described above,  
19 utilizing, for example, 2-trimethylsilylethyl 4-hydroxybenzoate. The  
20 latter reactions are not shown in **Reaction Scheme 12** but specific  
21 examples are described below.

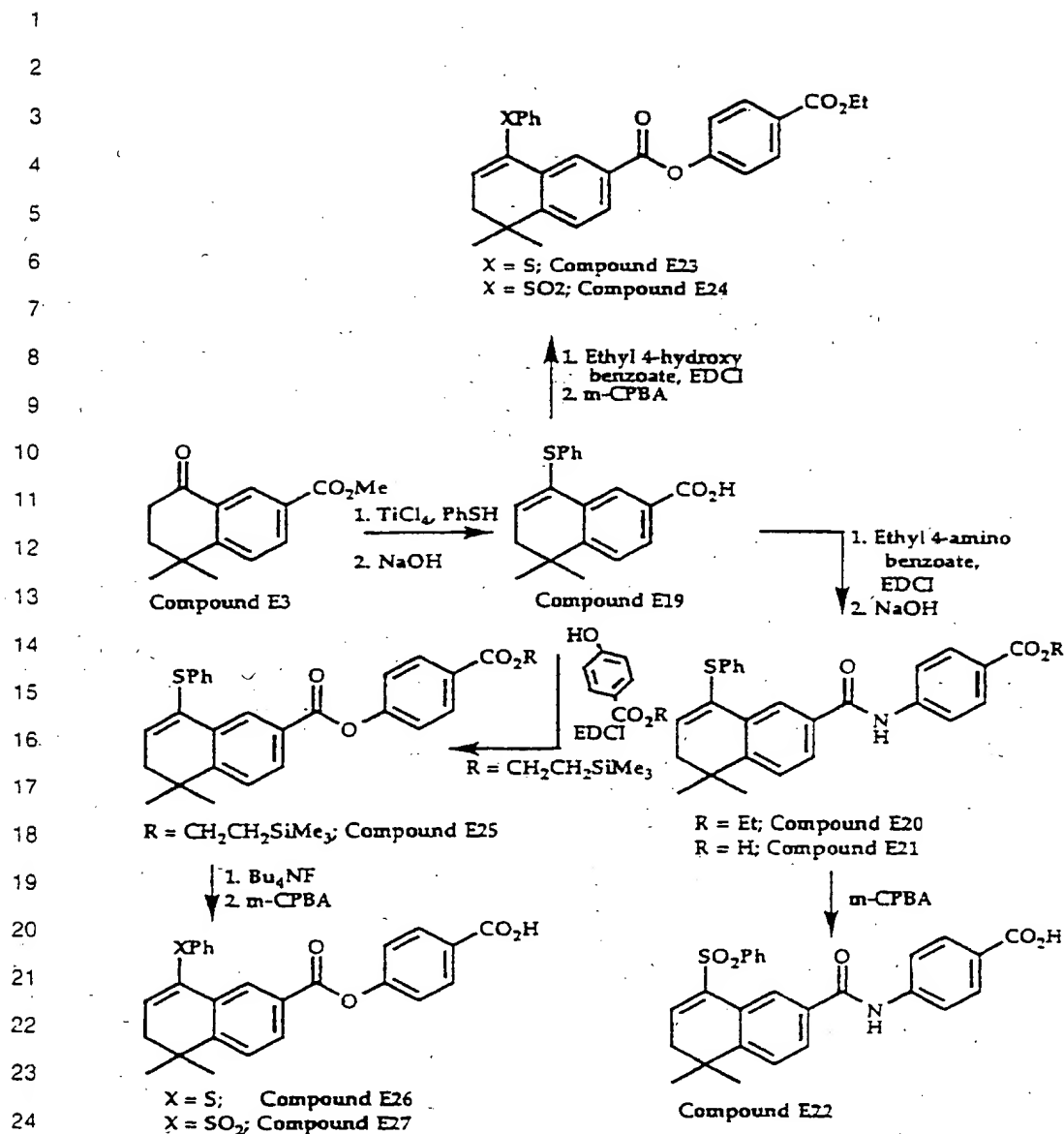
22 5,5-Dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-carboxylic acid  
23 (**Compound E3**) is also coupled with ethyl 4-hydroxybenzoate to provide  
24 ethyl 4-[[[(5,5-dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-  
25 yl)carbonyl]oxy]benzoate (**Compound E44**) within the scope of **Formula**  
26 **2**. **Compound E44** is subjected to a *Reformatsky* reaction with ethyl  
27 bromoacetate to yield (+/-) ethyl 4-[[[(5,5-dimethyl-8-hydroxy-8-  
28 (carbethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate  
29 (**Compound E54**). Although the following reactions are not shown in  
30 the scheme, an additional preferred example of compounds of the  
31 invention is obtained when **Compound E44** is reduced with sodium

borohydride to give ethyl 4-[[[(5,5-dimethyl-5,6,7,8-tetrahydro-8-hydroxy-naphthalen-2-yl)carbonyl]oxy]-benzoate (Compound E40). The latter is converted into tetrahydropyranyl derivatives (within the scope of **Formula 1**) as is disclosed in detail in the Specific Examples.

To obtain still more specific examples for the compounds of the invention where the Z group is -COO- or -CONH- 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**) is subjected to a *Reformatsky* reaction with ethyl bromoacetate, and the resulting (+/-) ethyl 2-(1-hydroxy-1,2,3,4-tetrahydro-4,4-dimethyl-7-bromo-naphthalen-1-yl)acetate (**Compound 47**) is subjected to the series of reactions shown in **Reaction Scheme 12**. These compounds, although not specifically shown in the scheme, are disclosed in detail in the appended Specific Examples.



Reaction Scheme 13



## Reaction Scheme 14

27 Reaction Scheme 13 discloses examples for the synthesis of several  
28 preferred compounds of the invention within the scope of Formula 3.

29 The reactions shown in this scheme are analogous to the reactions  
30 disclosed in the foregoing description and reaction schemes and  
31 therefore will be readily understood by those skilled in the art and do

1 not require further explanation here. A detailed experimental  
2 description for the preparation of compounds shown in this scheme is  
3 provided in the description of the Specific Examples. The same applies  
4 to **Reaction Scheme 14**, which discloses examples for the synthesis of  
5 several preferred compounds of the invention within the scope of  
6 **Formula 5**:

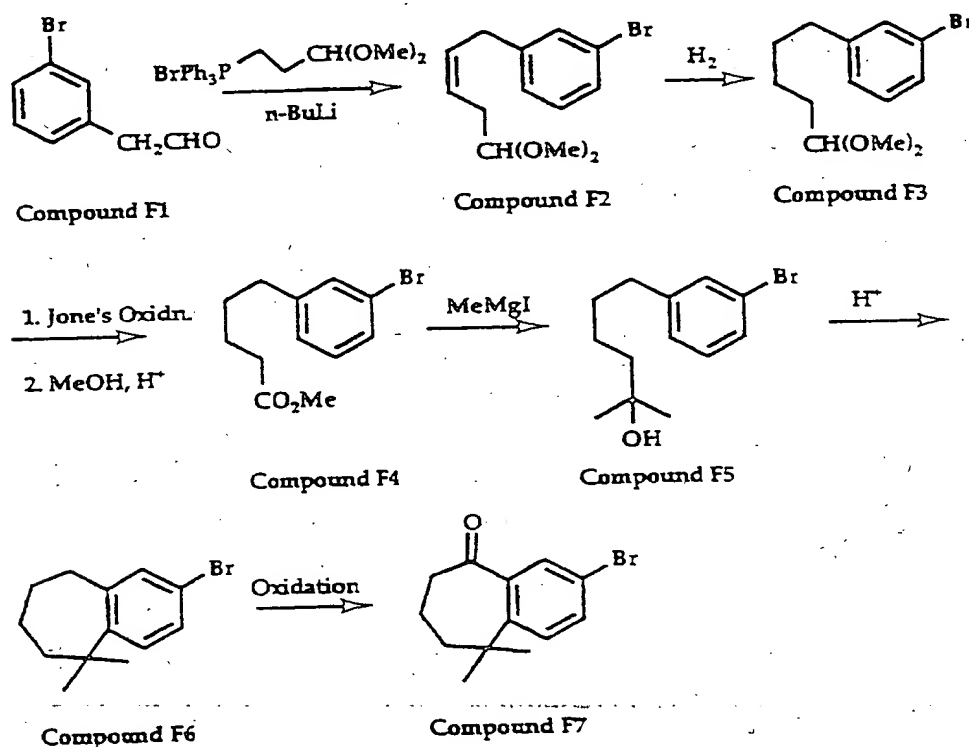
7 Compounds of the invention where with reference to the **Formulas 1**  
8 - **6** the **Z** group is  $\text{-N(O)=N-}$  or  $\text{-N=N(O)-}$  can be prepared by  
9 oxidation of compounds where the **Z** group is  $\text{-N=N-}$ . A suitable  
10 oxidizing agent for this purpose is *meta*-chloroperoxybenzoic acid;  
11 typically both isomers of the azoxy compounds are formed in reactions  
12 using this agent.

13 Compounds of the present invention where with reference to  
14 **Formula 1 - 6**, **Z** is  $\text{-OCO-}$ ,  $\text{NR}_1\text{CO}$ , as well as the corresponding  
15 thioester and thioamide analogs, can be prepared from the  
16 intermediates having a bromo function on the aromatic portion of the  
17 tetrahydronaphthalene or dihydronaphthalene nucleus, for example such  
18 as **Compounds G, H, A35, A37, B15 and C42**. In these compounds the  
19 bromo function is replaced with an amino or hydroxyl group, in analogy  
20 to the teachings of United States Patent Nos. 5,324,744, the  
21 specification of which is expressly incorporated herein by reference.

22 Compounds of the present invention where with reference to  
23 **Formula 1 - 6**, **Z** is  $\text{-N=CR}_1\text{-}$  or  $\text{-CR}_1\text{=N-}$  will be readily recognized by  
24 those skilled in the art as *Schiff* bases. These compounds can be made  
25 by reaction between a primary amine and aldehyde or ketone. In order  
26 to obtain these compounds where the **Z** is  $\text{-N=CR}_1\text{-}$  an amine of the  
27 structure where the  $\text{NH}_2$  group is attached to the aromatic portion of  
28 the tetrahydronaphthalene or dihydronaphthalene nucleus, is reacted  
29 with an aldehyde or ketone of the structure  $\text{OCR}_1\text{-Y(R}_2\text{)-A-B}$ . An  
30 example for such an amine is **Compound D9**. *Schiff* bases of the  
31 structure where **Z** is  $\text{-CR}_1\text{=N-}$  can be obtained by reaction of an amine

of the formula  $\text{NH}_2\text{-Y(R}_2\text{)-A-B}$  with an aldehyde or ketone where the aldehyde or ketone function is attached to the aromatic portion of the tetrahydronaphthalene or dihydronaphthalene nucleus. Compounds D14a and D14b serve as examples.

Compounds of the present invention where with reference to Formula 1 - 6, the  $\text{X}_1$  group is  $[\text{C(R}_1\text{)}_2]_n$  and  $n$  is zero (0), can be made starting with 6-bromo-indan-1-one (or an appropriately substituted derivative). In these synthetic schemes 6-bromo-indan-1-one is used in analogy to 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G) as a starting material. 6-bromo-3,3-dimethyl-indan-1-one is available accordance with the chemical literature. (See Smith, J.G.,; Massicotte, M.P. Org. Prep. Proced. Int., 1978, 10 123-131.)



Reaction Scheme 15

1 Compounds of the invention where with reference to **Formula 1 - 6**,  
2 the  $X_1$  group is  $[C(R_1)_2]_n$  and  $n$  is 2 can be made from 8-bromo-2,3,4,5-  
3 tetrahydro-5,5-dimethyl-1-(2H)-suberan-one (**Compound F7**) which is  
4 used as a starting material in analogy to **Compound G**. **Compound F7**  
5 can be made in accordance with the reaction sequence shown in  
6 **Reaction Scheme 15**. As is shown in the scheme, (3-  
7 bromophenyl)acetaldehyde (**Compound F1**) is subjected to a *Wittig*  
8 reaction to obtain a 5 carbon chain attached to the aromatic nucleus,  
9 and the resulting **Compound F2** is hydrogenated and subjected to *Jones*  
10 oxidation followed by esterification, to provide methyl (3-bromophenyl)-  
11 pentanoate (**Compound F4**). **Compound F4** is reacted with a Grignard  
12 reagent to provide a tertiary alcohol (**Compound F5**), which is cyclized  
13 to provide 8-bromo-2,3,4,5-tetrahydro-5,5-dimethyl-suberan (**Compound**  
14 **F6**). **Compound F6** is oxidized with  $CrO_3$  to yield 8-bromo-2,3,4,5-  
15 tetrahydro-5,5-dimethyl-1-(2H)-suberan-one (**Compound F7**).

#### 16 SPECIFIC EXAMPLES

##### 17 Ethyl (4-bromophenyl)acetate (Compound A)

18 A solution of 43 g (200 mmol) of 4-bromophenylacetic acid and 0.2 g  
19 of conc.  $H_2SO_4$  in 470 ml of ethanol was refluxed for 16 hours. The  
20 reaction mixture was cooled to ambient temperature, stirred with 6 g of  
21 solid  $K_2CO_3$  for 30 minutes and then filtered. The filtrate was  
22 concentrated in vacuo, diluted with  $Et_2O$  (200 ml), washed with 10%  
23 aqueous  $NaHCO_3$  (10 ml) and brine (10 ml), dried over  $MgSO_4$  and  
24 concentrated in vacuo to give the title compound as a colorless oil.  
25 PMR ( $CDCl_3$ ):  $\delta$  1.25 (3H, t,  $J = 7.0$  Hz), 3.56 (2H, s), 4.15 (2H, q,  $J$   
26  $= 7.0$  Hz), 7.16 (2H, d,  $J = 8.4$  Hz), 7.45 (2H, d,  $J = 8.4$  Hz).

##### 27 Ethyl (3-bromophenyl)acetate (Compound B)

28 Employing the same general procedure as for the preparation of  
29 ethyl (4-bromophenyl)acetate (**Compound A**), 100 g (463 mmol) of  
30 3-bromophenylacetic acid was converted into the title compound (yellow  
31 oil) using 2 g of conc.  $H_2SO_4$  and 500 ml of ethanol.

1 PMR ( $\text{CDCl}_3$ ) :  $\delta$  1.26 (3H, t,  $J = 7.0$  Hz), 3.56 (2H, s), 4.16 (2H, q,  $J = 7.0$  Hz), 7.16-7.26 (2H, m), 7.38-7.46 (2H, m).

3 Ethyl 4-(4-bromophenyl)butanoate (Compound C)

4 To a cold solution ( $-78^\circ\text{C}$ ) of 15 g (62 mmol) of ethyl  
5 (4-bromophenyl)acetate (Compound A) in 150 ml of  $\text{CH}_2\text{Cl}_2$  was added  
6 dropwise (over a span of 1 hour) 65 ml (65 mmol) of  
7 diisobutylaluminum hydride (DIBAL-H, 1M solution in hexane). After  
8 the DIBAL-H addition was complete, the reaction was stirred at  $-78^\circ\text{C}$   
9 for an additional hour. The reaction was quenched by the dropwise  
10 addition of methanol (10 ml), followed by water (10 ml) and 10% HCl  
11 (40 ml). The mixture was then warmed to  $0^\circ\text{C}$ , stirred for 10 minutes  
12 and then washed with water (15 ml), 10% aqueous  $\text{NaHCO}_3$  (10 ml)  
13 and brine (10 ml). The organic phase was dried over  $\text{MgSO}_4$  and the  
14 solvent distilled off at ambient temperature to give crude  
15 (4-bromophenyl)acetaldehyde. To a cold solution ( $0^\circ\text{C}$ ) of this crude  
16 aldehyde in 150 ml of  $\text{CH}_2\text{Cl}_2$  was added a solution of 26 g (74.6 mmol)  
17 of (carbethoxymethylene)triphenylphosphorane in 50 ml of  $\text{CH}_2\text{Cl}_2$ . The  
18 mixture was stirred for 16 hours, concentrated in vacuo and purified by  
19 flash chromatography (silica, 10% EtOAc-hexane) to give ethyl  
20 4-(4-bromophenyl)but-2-enoate as a mixture of E:Z isomers. This  
21 isomeric mixture was dissolved in 150 ml of EtOAc and hydrogenated  
22 over 1 g of 10% Pd/C for 6 hours. The catalyst was filtered off and the  
23 filtrate concentrated in vacuo to give the title compound as a white  
24 solid.

25 PMR ( $\text{CDCl}_3$ ) :  $\delta$  1.26 (3H, t,  $J = 7.1$  Hz), 1.88-1.99 (2H, m), 2.31 (2H,  
26 t,  $J = 7.5$  Hz), 2.61 (2H, t,  $J = 7.5$  Hz), 4.28 (2H, q,  $J = 7.1$  Hz), 7.05  
27 (2H, d,  $J = 8.4$  Hz), 7.40 (2H, d,  $J = 8.4$  Hz).

28 Ethyl 4-(3-bromophenyl)butanoate (Compound D)

29 Employing the same general multistep preparation as for ethyl  
30 4-(4-bromophenyl)butanoate (Compound C), 60 g (246 mmol) of ethyl  
31 (3-bromophenyl)acetate (Compound B) was converted into the title

1 compound (oil) using 255 ml (255 mmol) of diisobutylaluminum hydride  
2 (DIBAL-H, 1M in hexane), 85.8 g (250 mmol) of  
3 (carbethoxymethylene)triphenylphosphorane and 1.7 g of 10% Pd/C.  
4 PMR (CDCl<sub>3</sub>) :  $\delta$  1.26 (3H, t, J = 7.1 Hz), 1.89-2.00 (2H, m), 2.31 (2H,  
5 t, J = 7.5 Hz), 2.63 (2H, t, J = 7.2 Hz), 4.15 (2H, q, J = 7.1 Hz),  
6 7.10-7.35 (4H, m).

7 5-(3-bromophenyl)-2-methylpentan-2-ol (Compound E)

8 To a cold solution (0 °C) of 17 g (63 mmol) of ethyl  
9 4-(3-bromophenyl)butanoate (Compound D) in 40 ml of THF was  
10 added 63 ml (189 mmol) of methylmagnesium bromide (3.0M solution  
11 in THF). The reaction was stirred at 0 °C for 2 hours, quenched by the  
12 slow addition of ice cold water (30 ml) followed by 10% HCl (30 ml)  
13 and then extracted with Et<sub>2</sub>O (4 x 60 ml). The combined organic layer  
14 was washed with 10% aqueous NaHCO<sub>3</sub> (10 ml), water (10 ml) and  
15 brine (10 ml), dried over MgSO<sub>4</sub> and concentrated in vacuo.  
16 Purification by Kugelrohr distillation gave the title compound as a  
17 colorless oil.

18 PMR (CDCl<sub>3</sub>) :  $\delta$  1.20 (6H, s), 1.43-1.55 (2H, m), 1.62-1.78 (2H, m),  
19 2.60 (2H, t, J = 6.0 Hz), 7.10-7.41 (4H, m).

20 6-Bromo-1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (Compound F)

21 15.0 g (58.3 mmol) of 5-(3-bromophenyl)-2-methylpentan-2-ol  
22 (Compound E) was cooled to 0 °C and then 2.8 ml of conc. H<sub>2</sub>SO<sub>4</sub> was  
23 added. The mixture was stirred for 2.5 hours, diluted with water (20  
24 ml) and extracted with Et<sub>2</sub>O (3 x 40 ml). The combined organic layers  
25 were washed with water, sat. aqueous NaHCO<sub>3</sub> and brine, dried over  
26 MgSO<sub>4</sub> and concentrated in vacuo. Purification by Kugelrohr  
27 distillation gave the title compound as a colorless oil.

28 PMR (CDCl<sub>3</sub>) :  $\delta$  1.25 (6H, s), 1.61-1.66 (2H, m), 1.74-1.82 (2H, m),  
29 2.73 (2H, t, J = 6.0 Hz), 7.16-7.26 (3H, m).

30 7-Bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G)

31 To a cold mixture (0 °C) of 209 g (200 mmol) of chromium trioxide,



1 100 ml (1.06 mol) of acetic anhydride and 200 ml (3.5 mol) of acetic  
2 acid was added a solution of 10 g (41.8 mmol) of 6-bromo-1,2,3,4-tet-  
3 rahydro-1,1-dimethylnaphthalene (**Compound F**) in 125 ml of benzene.  
4 The reaction mixture was stirred for 1 hour, quenched with ice cold  
5 water and extracted with Et<sub>2</sub>O (3 x 100 ml). The organic layer was dried  
6 over MgSO<sub>4</sub>, concentrated in vacuo, and purified by column  
7 chromatography (silica, 10% EtOAc-hexane) to give the title compound  
8 as a white solid.

9 PMR (CDCl<sub>3</sub>) :  $\delta$  1.28 (6H, s), 2.01 (2H, t, J = 6.0 Hz), 2.72 (2H, t, J =  
10 6.0Hz), 7.31 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 3.0, 9.0 Hz), 8.11  
11 (1H, d, J = 3.0 Hz).

12 6-Bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound H**)

13 Employing a published procedure (Mathur, N.C.; Snow, M.S. ;  
14 Young, K. M.; and Pincock, J. A. Tetrahedron, **41**, 1509-1516 (1985) ),  
15 ethyl 4-(4-bromophenyl)butanoate (**Compound C**) was converted into  
16 the title compound. Alternatively, the title compound can be obtained  
17 using similar reactions that were used to convert ethyl  
18 4-(3-bromophenyl)butanoate (**Compound D**) into  
19 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one (**Compound G**)  
20 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-naphthalen-8(7H)-one-2-  
21 yl)ethenyl]-benzoate  
22 (**Compound A2**)

23 To a solution of 520.0 mg (2.00 mmol) of 3,4-dihydro-4,4-dimethyl-7-  
24 bromo-naphthalen-1(2H)-one (**Compound G**), and 510.0 mg (2.90 mmol)  
25 of ethyl 4-vinylbenzoate in 4.0 mL of triethylamine (degassed by sparging  
26 with argon for 25 minutes), was added 124.0 mg (0.40 mmol) of tris(2-  
27 methylphenyl) phosphine, followed by 44.0 mg (0.20 mmol) of  
28 palladium(II)acetate. The resulting solution was heated to 95 °C for 2.5 h ,  
29 cooled to room temperature, and concentrated under reduced pressure.  
30 Purification by column chromatography (10% EtOAc / hexanes) afforded  
31 the title compound as a colorless solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.41 (t, J = 7.1 Hz, 3H), 1.41 (s, 6H), 2.04 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.5 Hz, 2H); 4.39 (q, J = 7.1 Hz, 2H), 7.20 (s, 2H), 7.45 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.69 dd, J = 2.0, 8.2 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 2.0 Hz, 1H).

(E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-oxo-2-naphthalenyl)ethenyl]-benzoic acid (Compound A2a)

Employing the same general procedure as for the preparation of (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl oxime)-2-naphthalenyl)ethenyl]-benzoic acid (Compound A4) 110 mg (0.32 mmol) of ethyl (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-oxo-2-naphthalenyl)ethenyl]-benzoate (Compound A2) was converted into the title compound using 1.0 mL (1.5 mmol) of LiOH (1.5 M aqueous solution) and 0.5 mL of methanol.

<sup>1</sup>H NMR (DMSO) δ 1.36 (s, 6 H), 1.96 (t, J = 6.7 Hz, 3 H); 2.69 (t, J = 6.7 Hz, 2 H), 7.35 (d, J = 16.4 Hz, 1 H), 7.49 (d, J = 16.4 Hz, 1 H), 7.58 (d, J = 8.4 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 2 H), 7.89 (overlapping d, 3 H), 8.05 (s, 1 H).

Ethyl (E)-4-[2-(5,5-dimethyl-5,6-dihydro-8(7H)-anti-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoate (Compound A3)

A solution of 298 mg (0.85 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (Compound A2), 290 mg (3.4 mmol) of methoxylamine hydrochloride and 610 mg (4.5 mmol) of sodium acetate in 7.0 mL of EtOH and 5.0 mL of tetrahydrofuran was stirred at ambient temperature for 96 h and refluxed for 3 h. An additional 0.24 g (1.8 mmol) of methoxylamine hydrochloride was added and the mixture refluxed for another 1 h. The mixture was concentrated *in vacuo*, the residue was diluted with water and extracted with EtOAc (2 x). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica, 5 % ethyl acetate in hexanes) to afford the title compound as a yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 6 H), 1.41 (t, J = 7.1 Hz, 3 H), 1.73 (t, J =

6.9 Hz, 2 H), 2.80 (t,  $J = 6.9$  Hz, 2 H), 4.04 (s, 3H), 4.39 (q,  $J = 7.1$  Hz, 2 H), 7.13 (d,  $J = 16.4$  Hz, 1 H), 7.22 (d,  $J = 16.4$  Hz, 1 H), 7.36 (d,  $J = 8.2$  Hz, 1 H), 7.50 (dd,  $J = 2.0, 8.2$  Hz, 1 H), 7.57 (d,  $J = 8.4$  Hz, 2 H), 8.03 (d,  $J = 8.4$  Hz, 2 H), 8.11 (d,  $J = 2.0$  Hz, 1 H).

(E)-4-[2-(5,5-Dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4)

To a solution of 183 mg (0.48 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoate (Compound A3) in 4.0 mL of tetrahydrofuran and 1.0 mL of methanol was added 1.0 mL (2.4 mmol) of LiOH (2.4 M aqueous solution). The mixture was stirred at ambient temperature for 19 h, and concentrated *in vacuo*. The residue was diluted with water and acidified to pH 1 with 10% HCl, and extracted with ethyl acetate (2x). The organic phase was washed with brine, dried with  $\text{MgSO}_4$  and concentrated *in vacuo*. Recrystallization of the crude product using acetonitrile afforded the title compound as white crystals.

$^1\text{H}$  NMR ( $\text{DMSO-}d_6$ ):  $\delta$  1.24 (s, 6 H), 1.66 (t,  $J = 6.6$  Hz, 2 H), 2.72 (t,  $J = 6.6$  Hz, 2 H), 3.95 (s, 1 H), 7.26 (d,  $J = 16.5$  Hz, 1 H), 7.44 (d,  $J = 8.2$  Hz, 1 H), 7.44 (d,  $J = 16.5$  Hz, 1 H), 7.67 (d,  $J = 8.2$  Hz, 1 H), 7.74 (d,  $J = 8.1$  Hz, 2 H), 7.92 (d,  $J = 8.1$  Hz, 2 H), 8.01 (s, 1 H).

Ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-ethyl oxime)-naphthalen-2-yl)ethenyl]-benzoate (Compound A5)

Employing the same general procedure as for the preparation of ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-naphthalen-2-yl)ethenyl]-benzoate (Compound A3) 146 mg (0.42 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-5,6, dihydronaphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (Compound A2) was converted into the title compound (white solid) using 167 mg (1.7 mmol) of ethoxylamine hydrochloride, 337 mg (2.5 mmol) of sodium acetate, 5.0 mL of EtOH and 1.0 mL of tetrahydrofuran.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.28 (s, 6 H), 1.35 (t,  $J = 7.1$  Hz, 3 H), 1.39 (t,  $J =$

1 7.1 Hz, 3 H), 1.71 (t,  $J = 6.9$  Hz, 2 H), 2.80 (t,  $J = 6.9$  Hz, 2 H), 4.27 (q,  $J$   
2 = 7.1 Hz, 2 H), 4.37 (q,  $J = 7.1$  Hz, 2 H), 7.11 (d,  $J = 16.4$  Hz, 1 H), 7.21  
3 (d,  $J = 16.4$  Hz, 1 H), 7.34 (d,  $J = 8.2$  Hz, 1 H), 7.48 (dd,  $J = 1.9, 8.2$  Hz,  
4 1 H), 7.55 (d,  $J = 8.4$  Hz, 2 H), 8.01 (d,  $J = 8.4$  Hz, 2 H), 8.11 (d,  $J = 1.9$   
5 Hz, 1 H).

6 (E)-4-[2-(5,5-Dimethyl-5,6,-dihydro-8(7H)-anti-(O-ethyl oxime)-naphthalen-  
7 2-yl)ethenyl]-benzoic acid (Compound A6)

8 Employing the same general procedure as for the preparation of (E)-4-  
9 [2-(5,5-dimethyl-5,6,-dihydro--8(7H)-anti-(O-methyl oxime)-naphthalen-2-  
10 yl)ethenyl]-benzoic acid (Compound A4) 81 mg (0.21 mmol) of ethyl (E)-  
11 4-[2-(5,5-dimethyl-5,6-dihydro-8(7H)-anti-(O-ethyl oxime)-naphthalen-2-  
12 yl)ethenyl]-benzoate (Compound A5) was converted into the title  
13 compound (white solid) using 1.0 mL (1.8 mmol) of LiOH (1.8 M aqueous  
14 solution).

15  $^1\text{H}$  NMR (Acetone- $\text{D}_6$ ):  $\delta$  1.30 (s, 6 H), 1.31 (t,  $J = 7.1$  Hz, 3 H), 1.73 (t,  $J$   
16 = 6.9 Hz, 2 H), 2.78 (t,  $J = 6.9$  Hz, 2 H), 4.23 (q,  $J = 7.1$  Hz, 2 H), 7.30  
17 (d,  $J = 16.4$  Hz, 1 H), 7.41 (d,  $J = 16.4$  Hz, 1 H), 7.41 (d,  $J = 8.2$  Hz, 1  
18 H), 7.66 (dd,  $J = 1.9, 8.2$  Hz, 1 H), 7.76 (d,  $J = 8.4$  Hz, 2 H), 8.03 (d,  $J =$   
19 8.4 Hz, 2 H), 8.15 (d,  $J = 1.9$  Hz, 1 H).

20 Ethyl (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(oxime)-naphthalen-2-  
21 yl)ethenyl]-benzoate (Compound A7)

22 Employing the same general procedure as for the preparation of ethyl  
23 (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-  
24 naphthalen-2-yl)ethenyl]-benzoate (Compound A3) 190 mg (0.55 mmol) of  
25 ethyl (E)-4-[2-(5,5-dimethyl-5,6-dihydronaphthalen-8(7H)-one-2-  
26 yl)ethenyl]-benzoate (Compound A2) was converted into the title  
27 compound using 152 mg (1.7 mmol) of hydroxylamine hydrochloride, 430  
28 mg (3.2 mmol) of sodium acetate, 6.0 mL of EtOH and 1.0 mL of  
29 tetrahydrofuran.

30  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.32 (s, 6 H), 1.41 (t,  $J = 7.1$  Hz, 3 H), 1.77 (t,  $J =$   
31 7.0 Hz, 2 H), 2.91 (t,  $J = 7.0$  Hz, 2 H), 4.39 (q,  $J = 7.1$  Hz, 2 H), 7.13 (d,

1  $J = 16.4$  Hz, 1 H), 7.20 (d,  $J = 16.4$  Hz, 1 H), 7.39 (d,  $J = 8.2$  Hz, 1 H),  
2 7.49 (m,  $J = 1.8$  Hz, 1 H), 7.53 (d,  $J = 8.4$  Hz, 2 H), 8.02 (d,  $J = 8.4$  Hz, 2  
3 H), 8.08 (d,  $J = 1.8$  Hz, 1 H), 8.48 (s, 1 H).

4 (E)-4-[2-(5,5-Dimethyl-5,6,-dihydronaphthalen-8(7H)-anti(oxime)-2-  
5 yl)ethenyl]-benzoic acid (Compound A8)

6 Employing the same general procedure as for the preparation of (E)-4-  
7 [2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(O-methyl oxime)-naphthalen-2-  
8 yl)ethenyl]-benzoic acid (Compound A4) 104 mg (0.29 mmol) of ethyl  
9 (E)-4-[2-(5,5-dimethyl-5,6,-dihydro-8(7H)-anti-(oxime)-naphthalen-2-  
10 yl)ethenyl]-benzoate (Compound A7) was converted into the title  
11 compound using 1.0 mL (1.5 mmol) of LiOH (1.5 M aqueous solution).  
12  $^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.24 (s, 6 H), 1.66 (t,  $J = 6.7$  Hz, 2 H), 1.71 (t,  $J$   
13  $= 6.7$  Hz, 2 H), 7.23 (d,  $J = 16.5$  Hz, 1 H), 7.41 (d,  $J = 8.3$  Hz, 1 H), 7.42  
14 (d,  $J = 16.5$  Hz, 1 H), 7.62 (dd,  $J = 1.7, 8.3$  Hz, 1 H), 7.73 (d,  $J = 8.5$  Hz,  
15 2 H), 7.92 (d,  $J = 8.5$  Hz, 2 H), 8.03 (d,  $J = 1.7$  Hz, 1 H).

16 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(trifluoromethylsulfonyl)oxy-  
17 naphthalen-2-yl)ethenyl]-benzoate (Compound A9)

18 To a cold ( $-78^\circ\text{C}$ ) solution of 440.0 mg (2.40 mmol) of sodium  
19 bis(trimethylsilyl)amide in 10.0 mL of THF was added 700.0 mg (2.00  
20 mmol) of ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-naphthalen-8(7H)-one-2-  
21 yl)ethenyl]-benzoate (Compound A2) as a solution in 25.0 mL of THF.  
22 After stirring at  $-78^\circ\text{C}$  for 1.5 h, 960.0 mg (2.40 mmol) of 2[*N,N*-bis  
23 trifluoromethylsulfonyl]amino]-5-chloropyridine was added in one portion.  
24 After 30 min, the solution was warmed to  $0^\circ\text{C}$  and stirred for 3 h. The  
25 reaction was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$ , and  
26 extracted with EtOAc. The combined extracts were washed with 5%  
27 aqueous NaOH, dried ( $\text{NaSO}_4$ ), and the solvents removed under reduced  
28 pressure. The title compound was isolated as a colorless solid after column  
29 chromatography (7% EtOAc / hexanes).

30  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.32 (s, 6H), 1.41 (t,  $J = 7.1$  Hz, 3H), 2.43 (d,  $J = 4.9$   
31 Hz, 2H), 4.39 (q,  $J = 7.1$  Hz, 2H), 6.00 (t,  $J = 4.9$  Hz, 1H), 7.10 (d,  $J =$

1 16.4 Hz, 1H), 7.20 (d,  $J = 16.4$  Hz, 1H), 7.33 (d,  $J = 8.0$  Hz, 1H), 7.49 (d,  
2  $J = 8.0$  Hz, 1H), 7.52 (s, 1H), 7.57 (d,  $J = 8.4$  Hz, 2H), 8.04 (d,  $J = 8.4$  Hz,  
3 1H).

4 Ethyl (E)-4-[2-(5,5-dimethyl-8-(thiazol-2-yl)-5,6-dihydronaphthalen-2-  
5 yl)ethenyl]-benzoate (Compound A10)

6 To a cold ( $-78^{\circ}\text{C}$ ) solution of thiazole (0.38 g (0.10 mL, 1.4 mmol) in  
7 THF (2.0 mL) was added n-butyl lithium (1.6 M solution in hexanes, 0.5  
8 mL, 0.8 mmol) and stirred for 30 min. To this solution was added 0.176 g  
9 (1.3 mmol) of zinc chloride in 3.0 mL of tetrahydrofuran and stirred for 45  
10 min. The resulting turbid solution was transferred, via cannula, to a flask  
11 containing a mixture of 0.17 g (0.35 mmol) of ethyl (E)-4-[2-(5,5-  
12 dimethyl-8-(trifluoromethylsulfonyl)oxy-5,6-dihydronaphthalen-2-yl)ethenyl]  
13 benzoate (Compound A9) and 15 mg (0.01 mmol) of  
14 tetrakis(triphenylphosphine)palladium(0) in 3.0 mL of tetrahydrofuran. The  
15 reaction mixture was stirred for 1 h at ambient temperature and 1.5 h at 55  
16  $^{\circ}\text{C}$ . The reaction mixture was treated with aqueous  $\text{NH}_4\text{Cl}$ , and extracted  
17 with EtOAc (2 x). The combined organic layer was washed with brine and  
18 dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure and the  
19 crude product was purified by flash chromatography (silica, 20% ethyl  
20 acetate in hexane) to afford the title compound as a white solid.

21  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.34 (s, 6 H), 1.40 (t,  $J = 7.1$  Hz, 3 H), 2.41 (d,  $J =$   
22 4.9 Hz, 2 H), 4.37 (q,  $J = 7.1$  Hz, 2 H), 6.56 (t,  $J = 4.9$  Hz, 1 H), 7.03 (d,  
23  $J = 16.4$  Hz, 1 H), 7.18 (d,  $J = 16.4$  Hz, 1 H), 7.34 (d,  $J = 3.4$  Hz, 1 H),  
24 7.38 (d,  $J = 8.1$  Hz, 1 H), 7.48 (dd,  $J = 1.8, 8.4$  Hz, 1 H), 7.53 (d,  $J = 8.4$   
25 Hz, 2 H), 7.86 (d,  $J = 1.8$  Hz, 1 H), 7.93 (d,  $J = 3.4$  Hz, 1 H), 8.00 (d,  $J$   
26  $= 8.4$  Hz, 2 H).

27 (E)-4-[2-(5,5-Dimethyl-8-(thiazol-2-yl)-5,6-dihydronaphthalen-2-  
28 yl)ethenyl]-benzoic acid (Compound A12)

29 Employing the same general procedure as for the preparation of (E)-4-[2-  
30 (5,5-dimethyl-5,6-dihydro-8(7H)-anti-(O-methyl oxime)-naphthalen-2-  
31 yl)ethenyl]-benzoic acid (Compound A4), 20 mg (0.05 mmol) of ethyl

1 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(thiazol-2-yl)-naphthalen-2-yl)ethenyl]-  
2 benzoate (**Compound A10**) was converted into the title compound (white  
3 solid).

4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.28 (s, 6 H), 2.39 (d,  $J = 4.9$  Hz, 2 H), 6.63 (t,  $J =$   
5 4.9 Hz, 1 H), 7.15 (d,  $J = 16.4$  Hz, 1 H), 7.36 (d,  $J = 16.4$  Hz, 1 H), 7.43  
6 (d,  $J = 8.2$  Hz, 1 H), 7.63 (d,  $J = 8.2$  Hz, 1 H), 7.70 (d,  $J = 8.2$  Hz, 2 H),  
7 7.77 (d,  $J = 3.3$  Hz, 1 H), 7.90 (m,  $J = 8.2$  Hz, 3 H), 7.97 (d,  $J = 3.3$  Hz, 1  
8 H).

9 Ethyl (E)-4-[2-(5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-  
10 yl)ethenyl]-benzoate (**Compound A13**)

11 A solution of lithiothiophene was prepared by the addition of 0.10 g  
12 (0.095 mL, 1.2 mmol) of thiophene to a cold solution ( $-78^\circ\text{C}$ ) of 0.61 g  
13 (0.90 mL, 1.4 mmol, 1.6 M in hexanes) of n-butyl lithium in 2.0 mL of  
14 tetrahydrofuran. The solution was stirred at  $-78^\circ\text{C}$  for 35 min and then a  
15 solution of 0.158 g (1.2 mmol) of zinc chloride in 2.0 mL of  
16 tetrahydrofuran was added. The resulting solution was stirred at  $-78^\circ\text{C}$  to  
17 room temperature for 1 h and then the organozinc was added via cannula to  
18 a mixture of 0.212 g (0.44 mmol) of ethyl (E)-4-[2-(5,5-dimethyl-8-  
19 (trifluoromethylsulfonyl)oxy-5,6-dihydronaphthalen-2-yl)ethenyl] benzoate  
20 (Compound A9) and 18 mg (0.016 mmol) of  
21 tetrakis(triphenylphosphine)palladium(0) in 2.0 mL of tetrahydrofuran. The  
22 resulting mixture was stirred at room temperature for 10 min and then  
23 heated at  $50^\circ\text{C}$  for 1 h. The reaction was quenched by the addition of sat.  
24 aqueous  $\text{NH}_4\text{Cl}$ . The mixture was extracted with EtOAc (2x), and washed  
25 with brine. The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and then  
26 concentrated *in vacuo*. The crude material product was purified by flash  
27 chromatography (silica, 15 % ethyl acetate in hexanes) to afford the title  
28 compound as a solid.

29  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.34 (s, 6 H), 1.40 (t,  $J = 7.1$  Hz, 3 H), 2.34 (d,  $J =$   
30 4.8 Hz, 2 H), 4.37 (q,  $J = 7.1$  Hz, 2 H), 6.22 (t,  $J = 4.8$  Hz, 1 H), 7.02 (d,  
31  $J = 16.4$  Hz, 1 H), 7.10- 7.12 (m, 2 H), 7.15 (d,  $J = 16.4$  Hz, 1 H), 7.29-

1 7.33 (m, 1 H), 7.37 (d,  $J = 8.0$  Hz, 1 H), 7.45 (dd,  $J = 1.8, 8.0$  Hz, 1 H),  
2 7.52 (d,  $J = 8.5$  Hz, 2 H), 7.53 (d,  $J = 1.8$  Hz, 1 H), 8.00 (d,  $J = 8.4$  Hz, 2  
3 H).

4 (E)-4-[2-(-5,5-Dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-yl)ethenyl]-  
5 benzoic acid (Compound A15)

6 Employing the same general procedure as for the preparation of (E)-4-[2-  
7 (5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
8 yl)ethenyl]-benzoic acid (Compound A4) 98 mg (0.24 mmol) of ethyl (E)-  
9 4-[2-(-5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-yl)ethenyl]-  
10 benzoate (Compound A13) was converted into the title compound (white  
11 solid).

12  $^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.27 (s, 6H), 2.32 (d,  $J = 4.8$  Hz, 2 H), 6.23 (t,  $J$   
13  $= 4.8$  Hz, 1 H), 7.14 (d,  $J = 16.4$  Hz, 1 H), 7.14- 7.15 (overlapping d, 2  
14 H), 7.36 (d,  $J = 16.4$  Hz, 1 H), 7.43 (d,  $J = 8.1$  Hz, 1 H), 7.48 (d,  $J = 1.7$   
15 Hz, 1 H), 7.54 (t,  $J = 3.1$  Hz, 1 H), 7.62 (dd,  $J = 1.7, 8.1$  Hz, 1 H), 7.68  
16 (d,  $J = 8.4$  Hz, 2 H), 7.88 (d,  $J = 8.4$  Hz, 2 H).

17 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-  
18 naphthalenyl)ethenyl] benzoate (Compound A16)

19 To a degassed solution of 0.35 g (1.0 mmol) of 2-bromo-5,6-dihydro-  
20 5,5-dimethyl-8-(phenylthio)-naphthalene (Compound A35) and 0.34 g (1.9  
21 mmol) of ethyl 4-vinylbenzoate in 4.0 mL of triethylamine, was added  
22 0.066 g (0.2 mmol) of tri-*o*-tolylphosphine and then 0.025 g (0.1 mmol) of  
23 palladium(II) acetate. The reaction was heated at 90 °C for 2.25 h. The  
24 reaction was concentrated *in vacuo*. The residue was purified by flash  
25 chromatography (silica, 5 % ethyl acetate in hexane), followed by  
26 recrystallization using EtOH to afford the title compound as white crystals.

27  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 6 H), 1.40 (t,  $J = 7.1$  Hz, 3 H), 2.41 (d,  $J =$   
28 4.7 Hz, 2-H), 4.38 (q,  $J = 7.1$  Hz, 2 H), 6.55 (t,  $J = 4.7$  Hz, 1 H), 6.93 (d,  
29  $J = 16.3$  Hz, 1 H), 7.08-7.16 (m, 2 H), 7.22-7.27 (m, 6 H), 7.32 (d,  $J = 8.2$   
30 Hz, 1 H), 7.38 (dd,  $J = 1.7, 8.0$  Hz, 1 H), 7.49 (d,  $J = 8.4$  Hz, 2 H), 7.81  
31 (d,  $J = 1.7$  Hz, 1 H), 8.00 (d,  $J = 8.4$  Hz, 2 H).



1 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylsulfonyl)-  
2 naphthalenyl)ethenyl] benzoate (Compound A17)

3 To a solution of 0.090 g (0.2 mmol) of ethyl (E)-4-[2-(5,6-dihydro-5,5-  
4 dimethyl-8-(phenylthio)-naphthalenyl)ethenyl] benzoate (Compound A16)  
5 in 2.0 mL of methylene chloride was added dropwise a solution of 140 mg  
6 (0.45 mmol, 50-60 %) of m-chloroperoxybenzoic acid in 2.0 mL of  
7 methylene chloride and the reaction stirred at room temperature for 3.5 h.  
8 The mixture was diluted with water and extracted with methylene chloride  
9 (2x). The organic phase was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*.  
10 The crude product was purified by flash chromatography (silica, 30 % ethyl  
11 acetate in hexanes) followed by recrystallization in EtOH to afford the title  
12 compound as a solid.

13  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.22 (s, 6 H), 1.42 (t,  $J = 7.1$  Hz, 3 H), 2.50 (d,  $J =$   
14 4.9 Hz, 2 H), 4.39 (q,  $J = 7.1$  Hz, 2 H), 7.00 (d,  $J = 16.4$  Hz, 1 H), 7.13  
15 (d,  $J = 16.4$  Hz, 1 H), 7.29 (d,  $J = 8.4$  Hz, 1 H), 7.40 (dd,  $J = 1.7, 8.1$  Hz,  
16 1 H), 7.46-7.57 (m, 6 H), 7.97 (m, 2 H), 8.04 (d,  $J = 8.4$  Hz, 2 H), 8.11  
17 (d,  $J = 1.7$  Hz, 1 H).

18 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-naphthalen-2-yl)ethenyl]  
19 benzoic acid (Compound A18)

20 Employing the same general procedure as for the preparation of (E)-4-  
21 [2-(5,5-dimethyl-5,6-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
22 yl)ethenyl]-benzoic acid (Compound A4), 60 mg (0.14 mmol) of ethyl  
23 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylthio)-naphthalen-2-yl)ethenyl]  
24 benzoate (Compound A16) was converted into the title compound (white  
25 solid).

26  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.29 (s, 6 H), 2.40 (d,  $J = 4.6$  Hz, 3 H), 6.61 (t,  $J$   
27 = 4.6 Hz, 1 H), 7.05 (d,  $J = 16.4$  Hz, 1 H), 7.17-7.20 (m, 1 H), 7.28-7.35  
28 (m, 4 H), 7.38 (d,  $J = 8.1$  Hz, 1 H), 7.52 (dd,  $J = 1.6, 8.1$  Hz, 1 H), 7.67  
29 (d,  $J = 8.4$  Hz, 2 H), 7.73 (d,  $J = 1.6$  Hz, 1 H), 7.90 (d,  $J = 8.4$  Hz, 2 H).

30 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(phenylsulfonyl)-naphthalenyl)ethenyl]  
31 benzoic acid (Compound A19)

1 To a cold solution (0 °C) of 61 mg (0.15 mmol) of (E)-4-[2-(5,6-  
2 dihydro-5,5-dimethyl-8-(phenylthio)-naphthalen-2-yl)ethenyl] benzoic acid  
3 (**Compound A18**) in 5.0 mL of methylene chloride and 2.0 mL of  
4 tetrahydrofuran was added dropwise a cold solution (0 °C) of 70 mg (0.22  
5 mmol, 50-60%) of m-chloroperoxybenzoic acid in 4.0 mL of methylene  
6 chloride and the reaction stirred at 0 °C for 7 min. The mixture was diluted  
7 with water and extracted with methylene chloride (2x). The organic phase  
8 was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Recrystallization from  
9 acetonitrile gave the title compound as a solid.

10 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.16 (s, 6 H), 2.54 (d, *J* = 4.6 Hz, 2 H), 7.08 (d,  
11 *J* = 16.4 Hz, 1 H), 7.35-7.41 (m, 2 H), 7.48 (t, *J* = 4.6 Hz, 1 H), 7.56 (d, *J*  
12 = 8.7 Hz, 1 H), 7.63-7.68 (m, 3 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 7.93-7.96  
13 (m, 3 H), 8.03 (d, *J* = 8.2 Hz, 2 H).

14 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-  
15 yl)ethenyl] benzoate (**Compound A20**)

16 To a degassed solution of 0.50 g (1.7 mmol) of 2-bromo-5,6-dihydro-  
17 5,5-dimethyl-8-(ethylthio)-naphthalene (**Compound A36**) and 0.45 g (2.5  
18 mmol) of ethyl 4-vinylbenzoate in 4.0 mL of triethylamine, was added 109  
19 mg (0.36 mmol) of tri-*o*-tolylphosphine and then 35 mg (0.16 mmol) of  
20 palladium(II) acetate. The reaction was heated at 90 °C for 2.25 h. The  
21 reaction was concentrated *in vacuo* and purified by flash chromatography  
22 (silica, 2 % ethyl acetate in hexane) to afford the title compound as a  
23 colorless oil.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 6 H), 1.30 (t, *J* = 7.4 Hz, 3 H), 1.41 (t, *J* = 7.1  
25 Hz, 3 H), 2.31 (d, *J* = 4.8 Hz, 2 H), 2.75 (q, *J* = 7.4 Hz, 2 H), 4.38 (q, *J* =  
26 7.1 Hz, 2 H), 6.20 (t, *J* = 4.8 Hz, 1 H), 7.12 (d, *J* = 16.3 Hz, 1 H), 7.24  
27 (d, *J* = 16.3 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.41 (dd, *J* = 1.7, 8.0 Hz,  
28 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.89 (d, *J* = 1.7 Hz, 1 H), 8.02 (d, *J* = 8.4  
29 Hz, 2 H).

30 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-yl)ethenyl]  
31 benzoic acid (**Compound A21**)

1 Employing the same general procedure as for the preparation of (E)-4-[2-  
2 (5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
3 yl)ethenyl]-benzoic acid (**Compound A4**), 206 mg (0.52 mmol) of ethyl  
4 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-yl)ethenyl]  
5 benzoate (**Compound A20**) was converted into the title compound (white  
6 solid).

7 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.22 (t, *J* = 7.1 Hz, 3 H), 1.23 (s, 6 H), 2.27 (d, *J*  
8 = 4.9 Hz, 2 H), 2.75 (q, *J* = 7.1 Hz, 2 H), 6.15 (t, *J* = 4.9 Hz, 1 H), 7.24  
9 (d, *J* = 16.4 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 16.4 Hz, 1  
10 H), 7.75 (m, 3 H), 7.92 (d, *J* = 8.1 Hz, 2 H).

11 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(ethylsulfonyl)-naphthalen-2-  
12 yl)ethenyl] benzoate (**Compound A22**)

13 To a cold solution (0 °C) of 44 mg (0.12 mmol) of ethyl (E)-4-[2-(5,6-  
14 dihydro-5,5-dimethyl-8-(ethylthio)-naphthalen-2-yl)ethenyl] benzoic acid  
15 (**Compound A21**) in 4.0 mL of methylene chloride and 0.5 mL of  
16 tetrahydrofuran was added dropwise a cold solution (0 °C) of 55 mg (0.18  
17 mmol, 50-60%) of *m*-chloroperoxybenzoic acid in 3.0 mL of methylene  
18 chloride and the reaction stirred at 0 °C for 30 min. The mixture was  
19 diluted with water and extracted with methylene chloride (2x). The organic  
20 phase was diluted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated *in*  
21 *vacuo*. Recrystallization from acetonitrile gave the title compound as a  
22 solid.

23 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>): δ 1.16 (t, *J* = 7.3 Hz, 1 H), 1.25 (s, 6 H), 2.50 (d, *J*  
24 = 4.8 Hz, 2 H), 3.32 (q, *J* = 7.3 Hz, 2 H), 7.18 (t, *J* = 4.8 Hz, 1 H), 7.25  
25 (d, *J* = 16.4 Hz, 1 H), 7.46 (d, *J* = 16.4 Hz, 1 H), 7.49 (d, *J* = 8.1 Hz, 1  
26 H), 7.71 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.94 (d, *J* =  
27 8.4 Hz, 2 H), 8.04 (d, *J* = 1.5 Hz, 1 H).

28 Ethyl (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(1,3-dithian-2-  
29 yl)naphthalen-2-yl)ethenyl] benzoate (**Compound A23**)

30 To a cold solution (0 °C) of 140 mg (0.40 mmol) of ethyl (E)-4-[2-  
31 (5,5-dimethyl-5,6,-dihydro-naphthalen-8(7H)-one-2-yl)ethenyl]-benzoate

1 (Compound A2), in 6.0 mL of methylene chloride was added dropwise 130  
2 mg (0.12 mL, 1.2 mmol) of 1,3-propanedithiol and 0.17g (0.15 mL, 102  
3 mmol) of borontrifluoride diethyl etherate. The reaction stirred between 0  
4 °C and room temperature for 4 h. The mixture was diluted with aqueous  
5 sat. potassium carbonate, and extracted with ether (2x). The organic phase  
6 was washed with brine, dried over  $\text{MgSO}_4$  and then concentrated *in vacuo*.  
7 The crude product was purified by flash chromatography (silica, 10 % ethyl  
8 acetate in hexane) to afford the title compound as a solid.

9  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.29 (s, 6 H), 1.39 (t,  $J = 7.1$  Hz, 3 H), 1.83 (m, 2  
10 H), 2.00 (m, 1 H), 2.09 (m, 1 H), 2.62 (m, 2 H), 2.74 (m, 2 H), 3.17  
11 (m, 2 H), 4.36 (q,  $J = 7.1$  Hz, 2 H), 7.09 (d,  $J = 16.4$  Hz, 1 H), 7.20 (d,  $J$   
12 = 16.4 Hz, 1 H), 7.30 (d,  $J = 8.2$  Hz, 1 H), 7.41 (dd,  $J = 1.9, 8.2$  Hz, 1 H),  
13 7.55 (d,  $J = 8.4$  Hz, 2 H), 8.00 (d,  $J = 8.4$  Hz, 1 H), 8.10 (d,  $J = 1.9$  Hz, 2  
14 H).

15 (E)-4-[2-(5,6,7,8-Tetrahydro-5,5-dimethyl-8-(2-(1,3-dithian-2-  
16 yl)naphthalenyl)ethenyl]-benzoic acid (Compound A24)

17 Employing the same general procedure as for the preparation of (E)-4-[2-  
18 (5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
19 yl)ethenyl]-benzoic acid (Compound A4), 81 mg (0.18 mmol) of ethyl (E)-  
20 4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(1,3-dithian-2-yl)naphthalen-2-  
21 yl)ethenyl] benzoate (Compound A23) was converted into the title  
22 compound (white solid).

23  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  1.28 (s, 6 H), 1.83 (m, 2 H), 1.93 (m, 1 H), 2.19  
24 (m, 1 H), 2.66 (m, 4 H), 3.22 (m, 2 H), 7.18 (d,  $J = 16.4$  Hz, 1 H), 7.28  
25 (d,  $J = 16.4$  Hz, 1 H), 7.36 (d,  $J = 8.2$  Hz, 1 H), 7.48 (dd,  $J = 1.9, 8.2$  Hz,  
26 1 H), 7.66 (d,  $J = 8.4$  Hz, 2 H), 8.00 (d,  $J = 8.4$  Hz, 1 H), 8.12 (d,  $J = 1.9$   
27 Hz, 2 H).

28 Ethyl (E)-4-[2-(5,6-tetrahydro-5,5-dimethyl-8-(propyliden-2-yl)-naphthalen-  
29 2-yl)ethenyl]-benzoate (Compound A25)

30 To a degassed solution of 0.36 g (1.3 mmol) of 7-bromo-1(2H)-  
31 (propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound A37)

1 and 0.44 g (2.5 mmol) of ethyl 4-vinylbenzoate in 3.6 g (5.0 mL, 36 mmol)  
2 of triethylamine, was added 88 mg (0.29 mmol) of tri-*o*-tolylphosphine and  
3 then 33 mg (0.15 mmol) of palladium(II) acetate. The reaction was heated  
4 at 95 °C for 4 h. The reaction was concentrated *in vacuo* and purified by  
5 flash chromatography (silica, 1% ethyl acetate in hexane) to afford the title  
6 compound as an oil.

7 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 6 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.64 (t, *J* =  
8 6.8 Hz, 2 H), 1.89 (s, 3 H), 2.00 (s, 3 H), 2.51 (t, *J* = 6.8 Hz, 2 H), 4.38  
9 (q, *J* = 7.1 Hz, 2 H), 7.02 (d, *J* = 16.4 Hz, 1 H), 7.18-7.37 (overlapping d,  
10 3 H), 7.41 (s, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 8.02 (d, *J* = 8.4 Hz, 2 H).

11 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-(propyliden-2-yl)-naphthalen-2-  
12 yl)ethenyl]-benzoic acid (Compound A26)

13 Employing the same general procedure as for the preparation of (E)-4-[2-  
14 (5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
15 yl)ethenyl]benzoic acid (Compound A4) 95 mg (0.25 mmol) of ethyl (E)-  
16 4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(methylethyliden-2-yl)naphthalen-2-  
17 yl)ethenyl]benzoate (Compound A25) was converted into the title  
18 compound using 1.0 mL (2.3 mmol) of LiOH (2.3 M aqueous solution).

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 6 H), 1.64 (t, *J* = 6.9 Hz, 2 H), 1.86 (s, 3 H),  
20 2.02 (s, 3 H), 2.53 (t, *J* = 6.9 Hz, 2 H), 7.07 (d, *J* = 16.4 Hz, 1 H), 7.22-  
21 7.38 (overlapping d, 3 H), 7.42 (s, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 8.08 (d,  
22 *J* = 8.4 Hz, 2 H).

23 Ethyl (E)-4-[2-(7,8-dihydro-5,5-dimethyl-8(7H)-(pentyliden-3-yl)-  
24 naphthalen-2-yl)ethenyl]-benzoate (Compound A27)

25 To a degassed solution of 0.30 g (0.98 mmol) of 7-bromo-1(2H)-  
26 (pentyliden-3-yl)3,4-dihydro-4,4-dimethylnaphthalene (Compound A38) and  
27 0.17 g (0.97 mmol) of ethyl 4-vinylbenzoate in 3.63 g (5.0 mL, 36 mmol)  
28 of triethylamine, was added 61 mg (0.2 mmol) of tri-*o*-tolylphosphine and  
29 then 23 mg (0.10 mmol) of palladium(II) acetate. The reaction was heated  
30 at 95 °C for 6.5 h. The reaction was then concentrated *in vacuo* and  
31 purified by flash chromatography (silica, 100 % hexane) followed by

1 recrystallization from ethanol gave the title compound as white crystals.

2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.05 (t,  $J = 7.3$  Hz, 3 H), 1.20 (t,  $J = 7.4$  Hz, 3 H),  
3 1.24 (s, 6 H), 1.39 (t,  $J = 7.2$  Hz, 3 H), 1.65 (t,  $J = 6.8$  Hz, 2 H), 2.22 (q,  $J$   
4  $= 7.4$  Hz, 2 H), 2.31 (q,  $J = 7.3$  Hz, 2 H), 2.50 (t,  $J = 6.8$  Hz, 2 H), 4.36  
5 (q,  $J = 7.2$  Hz, 2 H), 7.04 (d,  $J = 16.4$  Hz, 1 H), 7.17 (d,  $J = 16.4$  Hz, 1  
6 H), 7.28 (d,  $J = 8.1$  Hz, 1 H), 7.34 (d,  $J = 8.1$  Hz, 1 H), 7.39 (s, 1 H), 7.53  
7 (d,  $J = 8.4$  Hz, 2 H), 8.00 (d,  $J = 8.4$  Hz, 2 H).

8 (E)-4-[2-(5,6-Dihydro-5,5-dimethyl-8(7H)-(pentyliden-3-yl)-naphthalen-2-  
9 yl)ethenyl]benzoic acid (Compound A28)

10 Employing the same general procedure as for the preparation of (E)-4-[2-  
11 (5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
12 yl)ethenyl]-benzoic acid (Compound A4), 150 mg (0.37 mmol) of ethyl  
13 (E)-4-[2-(5,6,-dihydro-5,5-dimethyl-8(7H)-(pentyliden-3-yl)-naphthalen-2-  
14 yl)ethenyl]-benzoate (Compound A27) was converted into the title  
15 compound (white solid).

16  $^1\text{H}$  NMR (Acetone- $\text{D}_6$ ):  $\delta$  1.08 (t,  $J = 7.4$  Hz, 3 H), 1.22 (t,  $J = 7.1$  Hz, 3  
17 H), 1.26 (s, 6 H), 1.67 (t,  $J = 7.1$  Hz, 3 H), 2.25 (q,  $J = 7.4$  Hz, 2 H), 2.33  
18 (q,  $J = 7.4$  Hz, 2 H), 2.50 (t,  $J = 7.1$  Hz, 2 H), 7.13 (d,  $J = 16.4$  Hz, 1 H),  
19 7.28 (d,  $J = 16.4$  Hz, 1 H), 7.31 (d,  $J = 8.6$  Hz, 1 H), 7.34 (m, 2 H), 7.62  
20 (d,  $J = 8.4$  Hz, 2 H), 7.98 (d,  $J = 8.4$  Hz, 2 H).

21 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-  
22 (cyclohexylidenyl)naphthalen-2-yl)ethenyl]-benzoate (Compound A29)

23 To a degassed solution of 0.40 g (1.3 mmol) of 7-bromo-1(2H)-  
24 (cyclohexylidenyl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound A39)  
25 and 0.62 g (3.5 mmol) of ethyl 4-vinylbenzoate in 2.2 g (3.0 mL, 22 mmol)  
26 of triethylamine, was added 76 mg (0.25 mmol) of tri-*o*-tolylphosphine and  
27 then 29 mg (0.13 mmol) of palladium(II) acetate. The reaction was heated  
28 at 95 °C for 2.5 h. The reaction was then concentrated *in vacuo* and  
29 purified by flash chromatography (silica, 1 % ethyl acetate in hexane) to  
30 afford the title compound as a white solid.

31  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.27 (s, 6 H), 1.39 (t,  $J = 7.1$  Hz, 3 H), 1.62 (m, 8

1 H), 2.34 (m, 2 H), 2.53 (m, 4 H), 4.37 (q,  $J = 7.1$  Hz, 2 H), 7.04 (d,  $J =$   
2 16.4 Hz, 1 H), 7.18 (d,  $J = 16.4$  Hz, 1 H), 7.28-7.35 (m, 3H), 7.53 (d,  $J =$   
3 8.4 Hz, 2 H), 8.01 (d,  $J = 8.4$  Hz, 2 H).

4 (E)-4-[2-(5,6-Dihydro-5,5-dimethyl-8(7H)-(cyclohexylidenyl)-naphthalen-2-  
5 yl)ethenyl]benzoic acid (Compound A31)

6 Employing the same general procedure as for the preparation of (E)-4-[2-  
7 (5,5-dimethyl-5,6,-dihydro-8(7H)-*anti*-(O-methyl oxime)-naphthalen-2-  
8 yl)ethenyl]-benzoic acid (Compound A4), 280 mg (0.68 mmol) of ethyl  
9 (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-(cyclohexylidenyl)-naphthalen-2-  
10 yl)ethenyl]benzoate (Compound A29) was converted into the title  
11 compound using 2.0 mL (3.3 mmol) of LiOH (1.7 M aqueous solution).  
12  $^1\text{H}$  NMR (DMSO- $\text{D}_6$ ):  $\delta$  1.28 (s, 6 H), 1.59-1.67 (m, 8 H), 2.36 (m, 2 H),  
13 2.48-2.57 (m, 4 H), 7.08 (d,  $J = 16.3$  Hz, 1 H), 7.20-7.38 (m, 5 H), 7.59 (d,  
14  $J = 8.4$  Hz, 1 H), 8.09 (d,  $J = 8.4$  Hz, 2 H).

15 (+/-) Ethyl (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-8-  
16 (methylcarbethoxy)naphthalen-2-yl)ethenyl] benzoate (Compound A32)

17 To a refluxing solution of 0.75 g ( 11.5 mmol) of granular zinc in 5.0  
18 mL of benzene was added a solution of ethyl (E)-4-[2-(5,5-dimethyl-5,6,-  
19 dihydro-naphthalen-8(7H)-one-2-yl)ethenyl]-benzoate (Compound A2) in  
20 5.0 mL of benzene followed by 0.27 g (0.18 mmol) of ethyl bromoacetate.  
21 The resulting mixture was refluxed for 24 h. The reaction was cooled,  
22 filtered through celite. The filtrate was washed with 10% HCl, sat. aqueous  
23  $\text{NaHCO}_3$  and brine. The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and  
24 concentrated *in vacuo*. The crude material was purified by flash  
25 chromatography (silica, 10 % ethyl acetate in hexane) to afford the title  
26 compound as a white solid.

27  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (t,  $J = 7.1$  Hz, 3 H), 1.30 ( 3H, s), 1.34 ( 3H, s),  
28 1.41 (t,  $J = 7.1$  Hz, 3 H), 1.77 (m, 2 H), 2.09 (m, 2 H), 2.82 (d,  $J = 3.4$  Hz,  
29 2 H), 4.17 (s, 1 H), 4.22 (q,  $J = 7.1$  Hz, 2 H), 4.38 (q,  $J = 7.1$  Hz, 2 H),  
30 7.10 (d,  $J = 16.4$  Hz, 1 H), 7.20 (d,  $J = 16.4$  Hz, 1 H), 7.31 (d,  $J = 8.2$  Hz,  
31 1 H), 7.42 (dd,  $J = 1.9, 8.2$  Hz, 1 H), 7.55 (d,  $J = 8.4$  Hz, 2 H), 7.75 (d,  $J$

1 = 1.9 Hz, 1 H), 8.03 (d,  $J$  = 8.4 Hz, 2 H).

2 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8-(methylcarbethoxy)naphthalen-2-  
3 yl)ethenyl]benzoate (Compound A33a)

4 Ethyl (E)-4-[2-(5,6-dihydro-5,5-dimethyl-8(7H)-anti  
5 (carbethoxymethylidenyl)-naphthalen-2-yl)ethenyl]benzoate (Compound  
6 A33b)

7 To a solution of 0.25 g (0.57 mmol) of (+/-)ethyl (E)-4-[2-(5,6,7,8-  
8 tetrahydro-5,5-dimethyl-8-hydroxy-8-(methylcarbethoxy)-naphthalen-2-  
9 yl)ethenyl] benzoate (Compound A32) in 11.0 mL of benzene was  
10 added 1.0 g (4.2 mmol) of *Burgess* reagent and the resulting solution was  
11 heated at 55°C for 30 min. The reaction was cooled and concentrated *in*  
12 *vacuo*, the residue was diluted with water and extracted with EtOAc (2 x),  
13 the organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and  
14 concentrated *in vacuo* to afford a mixture of title compounds in a 3:1 ratio  
15 (endo: exo). The title compounds were separated by flash chromatography  
16 (silica, 5 % ethyl acetate in hexane) to afford the pure isomers as white  
17 solids.

18 **Compound A33a:**

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.21 (t,  $J$  = 7.1 Hz, 3 H), 1.30 (s, 6H), 1.41 (t,  $J$  = 7.1  
20 Hz, 3 H), 2.82 (d,  $J$  = 4.3 Hz, 2 H), 3.51 (s, 2 H), 4.12 (q,  $J$  = 7.1 Hz, 2  
21 H), 4.38 (q,  $J$  = 7.1 Hz, 2 H), 5.97 (t,  $J$  = 4.3 Hz, 1 H), 7.05 (d,  $J$  =  
22 16.4 Hz, 1 H), 7.19 (d,  $J$  = 16.4 Hz, 1 H), 7.30-7.40 (m, 3 H), 7.47 (d,  $J$  =  
23 8.4 Hz, 2 H), 8.03 (d,  $J$  = 8.4 Hz, 2 H).

24 4,4-Dimethyl-7-bromo-1-phenylthio-3,4-dihydronaphthalene (Compound  
25 A35)

26 To a stirred solution of 4,4-dimethyl-7-bromo-3,4-dihydronaphthalen-  
27 1(2H)one (Compound G, 1.48 g, 5.9 mmol), titanium tetrachloride (1.09 g,  
28 5.7 mmol) and THF (10 mL) was added a mixture of thiophenol (660 mg, 6  
29 mmol), triethylamine (1.16 g, 11.5 mmol) and THF (20 mL) via an addition  
30 funnel at ambient temperature. The mixture was stirred for 5 h, and water  
31 (10 mL) was added, extracted with ether (3 X 50 mL). The combined



1 organic layer was washed successively with water (10 mL), 10% NaHCO<sub>3</sub>  
2 (10 mL) and brine (10 mL). The organic layer was dried (MgSO<sub>4</sub>) and the  
3 solvent distilled off at reduced pressure. After silicagel chromatography the  
4 title compound was obtained as a colorless oil.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 6H), 2.39 (d, J = 4.9 Hz, 2H), 6.54 (t, J =  
6 4.9 Hz, 1H), 7.10-7.35 (m, 7H), 7.78 (d, J = 2.0 Hz, 1H).

7 2-Bromo-5,6-dihydro-5,5-dimethyl-8-(ethylthio)-naphthalene (Compound  
8 A36)

9 To a solution of 1.03 g (4.1 mmol) of 7-bromo-3,4-dihydro-4,4-  
10 dimethylnaphthalen-1(2H)-one (Compound G) in 30.0 mL of  
11 tetrahydrofuran, was added dropwise 0.49 g (0.85 mL, 7.8 mmol) of  
12 titaniumtetrachloride and the resulting solution stirred for 10 min. A  
13 solution of 35 mg (0.50 mL, 6.7 mmol) of ethanethiol and 0.54 g (0.75  
14 mL, 5.4 mmol) of triethylamine in 10.0 mL of tetrahydrofuran was added  
15 and the reaction stirred at room temperature for 13 h. The mixture was  
16 diluted with water and extracted with ether (2x). The organic phase was  
17 washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated *in vacuo*.  
18 Purification by flash chromatography (silica, 100 % hexane) gave the title  
19 compound as an oil.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25 (s, 6 H), 1.27 (t, J = 7.1 Hz, 3 H), 2.29 (d, J =  
21 4.8 Hz, 2 H), 2.70 (q, J = 7.1 Hz, 2 H), 6.23 (t, J = 4.8 Hz, 1 H), 7.17 (d,  
22 J = 8.2 Hz, 1 H), 7.35 (dd, J = 1.7, 8.2 Hz, 1 H), 7.85 (d, J = 2.1 Hz, 2 H).

23 7-Bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
24 (Compound A37)

25 To a slurry of titanium trichloride (5 g, 32 mmol) in DME (80 mL) was  
26 added lithium wire in small portions (0.7 g, 100 mmol) under argon  
27 atmosphere. The mixture was refluxed for 1 h, cooled to ambient  
28 temperature and a solution of acetone (928 mg, 16 mmol) and 7-bromo-3,4-  
29 dihydro-4,4-dimethylnaphthalen-1(2H)-one (Compound G, 1.0 g, 3.96  
30 mmol) in 20 mL of DME was added. The resultant mixture was refluxed  
31 for 16 h under argon atmosphere. The reaction mixture was then cooled to

1 ambient temperature and diluted with hexane (100 mL), And thereafter  
2 filtered through a pad of florisil. The filtrate was concentrated under  
3 reduced pressure and purified by flash chromatography (silica, 100%  
4 hexane) to afford the title compound as a colorless oil.  
5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.19 (s, 6H), 1.56 (t,  $J = 6.9\text{Hz}$ , 2H), 1.81 (s, 3H),  
6 1.94 (s, 3H), 2.44 (t,  $J = 7.1\text{Hz}$ , 2H), 7.11 (d,  $J = 8.3\text{Hz}$ , 1H), 7.23 (dd,  $J =$   
7 2.1, 8.4Hz, 1H), 7.35 (d,  $J = 2.1\text{Hz}$ , 1H).

8 7-Bromo-1(2H)-(pentyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
9 **(Compound A38)**

10 Employing the same general procedure as for the preparation of 7-  
11 bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
12 **(Compound A37)**, 1.0 g (3.97 mmol) of 4,4-dimethyl-7-bromo-3,4-  
13 dihydronaphthalen-1(2H)one **(Compound G)** was converted into the  
14 title compound using 1.37 g (15.9 mmol) of 3-pentanone, 1.92 g (277  
15 mmol) of lithium and 12.2 g (79.4 mmol) of titanium trichloride.

16  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ):  $\delta$  1.04 (t,  $J = 7.5\text{ Hz}$ , 3H), 1.14 (t,  $J = 7.5\text{ Hz}$ ,  
17 3H), 1.23 (s, 6H), 1.63 (t,  $J = 7.1\text{ Hz}$ , 2H), 2.21 (q,  $J = 7.5\text{ Hz}$ , 2H),  
18 2.29 (q,  $J = 7.5\text{ Hz}$ , 2H), 2.49 (t,  $J = 7.1\text{ Hz}$ , 2H), 7.15 (d,  $J = 8.3$   
19 Hz, 1H), 7.29 (dd,  $J = 2.2, 8.3\text{ Hz}$ , 1H), 7.36 (d,  $J = 2.2\text{ Hz}$ , 1H).

20 7-Bromo-1(2H)-(cyclohexylidenyl)-3,4-dihydro-4,4-  
21 dimethylnaphthalene **(Compound A39)**

22 Employing the same general procedure as for the preparation of  
23 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
24 **(Compound A37)**, 1.0 g (3.97 mmol) of 4,4- dimethyl-7-bromo-3,4-  
25 dihydronaphthalen-1(2H)one **(Compound G)** was converted into the  
26 title compound using 1.56 g (15.9 mmol) of cyclohexanone, 1.92 g  
27 (277 mmol) of lithium and 12.2 g (79.4 mmol) of titanium trichloride.

28  $^1\text{H}$ MR ( $\text{CDCl}_3$ ):  $\delta$  1.23 (s, 6H), 1.50-1.65 (m, 8H), 2.33 (br s, 2H),  
29 2.45 (t,  $J = 5.5\text{ Hz}$ , 2H), 2.50 (t,  $J = 7.1\text{ Hz}$ , 2H), 7.15 (d,  $J = 8.1$   
30 Hz, 1H), 7.26 (d,  $J = 1.6\text{ Hz}$ , 1H), 7.29 (br s, 1H).

31 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-naphth-7-yl]naphth-2-oate

1 (Compound B1).

2 To a degassed solution of 0.39 g (1.4 mmol) of ethyl 6-bromo-  
3 naphthalene-2-carboxylate and 3.0 mL of toluene, was added  
4 sequentially 49 mg (0.04 mmol) of tetrakis-triphenylphosphine  
5 palladium(0), 2.0 mL (2.0 mmol) of 1M sodium carbonate and then a  
6 solution of 0.32 g (1.6 mmol) of (5,6,7,8-tetrahydro-5,5-  
7 dimethylnaphth-2-yl)boronic acid (Compound B13) in 3.0 mL of  
8 MeOH. The reaction was heated at 80 °C for 6 h, diluted with 2N  
9 Na<sub>2</sub>CO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x), the organic layer was  
10 washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to  
11 give an oil. Flash chromatography (silica, 5 % ethyl acetate in  
12 hexane) of the crude material gave the title compound as a white  
13 solid.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.35 (s, 6 H), 1.46 (t, J = 7.1 Hz,  
15 3 H), 1.70-1.74 (m, 2 H), 1.85-1.89 (m, 2 H), 2.88 (t, J = 6.3 Hz, 2  
16 H), 4.46 (q, J = 7.1 Hz, 2H), 7.42 (d, J = 1.7 Hz, 1 H), 7.46 (d, J  
17 = 8.2 Hz, 1 H), 7.52 (dd, J = 2.0, 8.2 Hz, 1 H), 7.80 (dd, J = 1.7,  
18 8.5 Hz, 1 H), 7.91 (d, J = 8.6 Hz, 1 H), 8.00 (d, J = 8.5 Hz, 1 H),  
19 8.05 (s, 1 H), 8.08 (dd, J = 1.7, 8.6 Hz, 1 H), 8.61 (s, 1 H).

20 6-[5,6,7,8-Tetrahydro-5,5-dimethyl-naphth-7-yl]-2-naphthoic acid

21 (Compound B2)

22 Employing the same general procedure as for the preparation of (E)-  
23 4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl oxime)-  
24 naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4) 50 mg (0.14  
25 mmol) of ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-naphth-7-yl]naphth-  
26 2-oate (Compound B1) was converted into the title compound (white  
27 solid).

28 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 300 MHz): δ 1.28 (s, 6 H), 1.64-1.68 (m, 2 H),  
29 1.77-1.80 (m, 2 H), 2.82 (t, J = 5.7 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 1  
30 H), 7.49 (s, 1 H), 7.58 (d, J = 8.4 Hz, 1 H), 7.89 (dd J = 1.8, 8.7 Hz,  
31 1 H), 7.98 (dd, J = 1.8, 8.7 Hz, 1 H), 8.05 (d, J = 8.7 Hz, 1 H), 8.17 (d,

1  $J = 8.7$  Hz, 1 H), 8.24 (s, 1 H), 8.60 (s, 1 H).

2 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(t-butyldimethylsilyloxy)-  
3 naphth-7-yl]naphth-2-oate (Compound B3)

4 To a degassed solution of 722 mg (2.6 mmol) of ethyl 6-bromo-  
5 naphthalenecarboxylate in 6.0 mL of toluene, was added sequentially  
6 90 mg (0.08 mmol) of tetrakis-triphenylphosphine palladium (0), 5.0  
7 mL (10.0 mmol) of 2M sodium carbonate, and a solution of 1.018 g  
8 (3.1 mmol) of (5,6,7,8-tetrahydro-5,5-dimethyl-8-(t-  
9 butyldimethylsilyloxy)naphth-2-yl)boronic acid (Compound B14) in  
10 3.0 mL of MeOH. The reaction was heated at 90 °C for 15 h. The  
11 reaction was diluted with 2N Na<sub>2</sub>CO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  
12 x), the organic layer was washed with brine, dried over MgSO<sub>4</sub>, and  
13 concentrated *in vacuo* to give an oil. The crude product was purified  
14 flash chromatography (silica, 5 % ethyl acetate in hexane) to afford  
15 the title compound as a white solid.

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  0.20 (s, 3 H), 0.23 (s, 3 H), 1.00 (s,  
17 9 H), 1.35 (s, 6 H), 1.46 (t, 3 H,  $J = 7.1$  Hz), 1.70-2.10 (m, 4 H), 4.46  
18 (q,  $J = 7.1$  Hz, 2H), 4.83 (dd,  $J = 4.7, 8.2$  Hz, 1 H), 7.42 (d,  $J = 8.2$   
19 Hz, 1 H), 7.60 (dd,  $J = 2.1, 8.2$  Hz, 1 H), 7.79-7.82 (overlapping s, dd,  
20 2 H), 7.90 (d,  $J = 8.7$  Hz, 1 H), 7.92 (d,  $J = 8.5$  Hz, 1 H), 8.06-8.1  
21 (overlapping s, dd, 2 H), 8.62 (s, 1 H).

22 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-naphth-7-  
23 yl]naphth-2-oate (Compound B4)

24 To a cold (0 °C) solution of 1.15 g (2.4 mmol) of ethyl-6-[5,6,7,8-  
25 tetrahydro-5,5-dimethyl-8-(t-butyldimethylsilyloxy)-naphth-7-  
26 yl]naphth-2-oate

27 (Compound B3) in 12.0 mL of tetrahydrofuran, was added 3.1 g

28 (12.0 mL, 12.0 mmol, 1.0-M in tetrahydrofuran) of

29 tetrabutylammoniumfluoride and the mixture was stirred between 0 °C  
30 to room temperature for 3 h. The reaction was then concentrated *in*  
31 *vacuo*, diluted with water, and extracted with ether (2 x), the organic

1 layer was washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in*  
2 *vacuo* to give a solid. Recrystallization from ethanol gave the title  
3 compound as a white solid.

4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.32 (s, 3 H), 1.39 (s, 3 H), 1.46 (t,  
5  $J = 7.1$  Hz, 3 H), 1.66-1.72 (m, 1 H), 1.90-1.99 (m, 3 H), 2.11-2.20 (m,  
6 1 H), 4.47 (q,  $J = 7.1$  Hz, 2H), 4.85 (t,  $J = 5.0$  Hz, 1H), 7.46 (d,  $J =$   
7 8.2 Hz, 1 H), 7.63 (dd,  $J = 2.1, 8.2$  Hz, 1 H), 7.81 (dd,  $J = 1.8, 8.7$  Hz,  
8 1 H), 7.83 (s, 1 H), 7.90 (d,  $J = 8.5$  Hz, 1 H), 8.00 (d,  $J = 8.7$  Hz, 1 H),  
9 8.08 (overlapping, 2 H), 8.61 (s, 1 H).

10 6-[5,6,7,8-Tetrahydro-5,5-dimethyl-8-hydroxy-naphth-7-yl]-2-  
11 naphthoic acid  
12 (Compound B5)

13 Employing the same general procedure as for the preparation of  
14 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-*anti*-(O-methyl oxime)-  
15 naphthalen-2-yl)ethenyl]-benzoic acid (Compound A4) 124 mg (0.33  
16 mmol) of ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-naphth-  
17 7-yl]naphth-2-oate (Compound B4) was converted into the title  
18 compound.

19  $^1\text{H}$  NMR (DMSO, 300 MHz):  $\delta$  1.25 (s, 3 H), 1.29 (s, 3 H), 1.58-  
20 1.99 (m, 4 H), 3.33 (s, 1 H), 4.62 (s, 1 H), 7.47 (d,  $J = 8.2$  Hz, 1  
21 H), 7.66 (dd,  $J = 2.0, 8.2$  Hz, 1 H), 7.85 (d,  $J = 2.0$  Hz, 1 H), 7.89  
22 (dd  $J = 1.7, 8.6$  Hz, 1 H), 8.00 (dd,  $J = 1.7, 8.6$  Hz, 1 H), 8.07 (d,  $J$   
23 = 8.6 Hz, 1 H), 8.19 (d,  $J = 8.6$  Hz, 1 H), 8.24 (s, 1 H), 8.61 (s, 1  
24 H).

25 Ethyl -6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-one-2-yl]-  
26 naphthalen-2-oate (Compound B6)

27 To a solution of 101 mg (0.27 mmol) of ethyl-6-[5,6,7,8-  
28 tetrahydro-5,5-dimethyl-8-hydroxy-naphth-7-yl]naphth-2-oate  
29 (Compound B4) in 1.5 mL of methylene chloride was added 50 mg  
30 (0.43 mmol) of N-methylmorpholine N-oxide and 6.0 mg (0.017  
31 mmol) of tetrapropylammonium perruthenate(VII). The reaction was

1 stirred at room temperature for 3 h, diluted with water, and extracted  
2 with CH<sub>2</sub>Cl<sub>2</sub> (2 x). The combined organic layer was washed with  
3 brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give a foam.  
4 The title compound was obtained as a white solid after flash  
5 chromatography (silica, 10% ethyl acetate in hexane).  
6 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.46 (overlapping s, 6 H), 1.46  
7 (overlapping t, *J* = 7.1 Hz, 3 H), 2.09 (t, *J* = 6.4 Hz, 2 H), 2.80 (t, *J*  
8 = 6.4 Hz, 2 H), 4.46 (q, *J* = 7.1 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 1 H),  
9 7.83 (dd, *J* = 1.8, 8.6 Hz, 1 H), 7.90-7.95 (several d, 2 H), 8.04 (d, *J*  
10 = 8.4 Hz, 1 H), 8.09-8.12 (overlapping s, dd, 2 H), 8.41 (d, *J* = 2.1  
11 Hz, 1 H), 8.63 (s, 1 H).

12 6-[5,5-Dimethyl-5,6-dihydro--naphthlen-8(7H)-one-2-yl]-2-naphthoic  
13 acid (Compound B7)

14 Employing the same general procedure as for the preparation of  
15 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl oxime)-2-  
16 naphthalenyl)ethenyl]-benzoic acid (Compound A4) 58 mg (0.16  
17 mmol) of ethyl 6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-one-2-  
18 yl]-naphthalen-2-oate (Compound B6) was converted into the title  
19 compound (white solid).

20 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 300 MHz): δ 1.41 (s, 6 H), 2.01 (t, *J* = 6.7  
21 Hz, 2 H), 2.74 (t, *J* = 6.7 Hz, 2 H), 7.71 (d, *J* = 8.3 Hz, 1 H),  
22 7.93 (dd, *J* = 1.8, 8.7 Hz, 1 H), 7.93 (dd, *J* = 1.7, 8.5 Hz, 1 H), 8.07-  
23 8.13 (several d, 3 H), 8.22 (d, *J* = 8.5 Hz, 1 H), 8.26 (s, 2 H), 8.32  
24 (s, 1 H), 8.63 (s, 1 H).

25 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(methoxymethyloxy)-  
26 naphth-7-yl]naphth-2-oate (Compound B8)

27 To a cold (0 °C) solution of 130 mg (0.35 mmol) of ethyl-6-  
28 [5,6,7,8-tetrahydro-5,5-dimethyl-8-(hydroxy)-naphth-7-yl]naphth-2-  
29 oate (Compound B4) in 2.0 mL of methylene chloride was added 50  
30 mg (0.15 mL, 0.86 mmol) of Hunig's base, followed by 0.21 g (0.20  
31 mL, 2.6 mmol) chloromethyl methyl ether was added and stirred at

1 room temperature for 14 h. About 500 mgs of t-butylammonium  
2 iodide was then added and the reaction was warmed to 35 °C for one  
3 additional hour. The reaction was diluted with water, and extracted  
4 with CH<sub>2</sub>Cl<sub>2</sub> (2 x). The combined organic layer was washed with  
5 brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give an oil.  
6 The title compound was obtained as an oil after flash chromatography  
7 (silica, 10 % ethyl acetate).

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.31 (s, 3 H), 1.40 (s, 3 H), 1.46 (t,  
9 3 H, *J* = 7.1 Hz), 1.60 (m, 1 H), 1.98-2.08 (m, 3 H), 3.51 (s, 3 H),  
10 4.46 (q, *J* = 7.1 Hz, 2H), 4.75 (t, *J* = 4.5 Hz, 1 H), 4.83 (d, *J* = 7.0  
11 Hz, 1 H), 4.93 (d, *J* = 7.0 Hz, 1 H), 7.48 (d, *J* = 8.2 Hz, 1 H),  
12 7.63 (dd, *J* = 2.0, 8.2 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H), 7.80 (dd *J*  
13 = 1.7, 8.5 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 1 H), 8.01 (d, *J* = 8.7 Hz, 1  
14 H), 8.05 (s, 1 H), 8.09 (dd, *J* = 1.7, 8.7 Hz, 1 H), 8.62 (s, 1 H).

15 6-[5,6,7,8-Tetrahydro-5,5-dimethyl-8-(methoxymethoxy)-naphth-7-  
16 yl]-2-naphthoic acid (Compound B9)

17 Employing the same general procedure as for the preparation of  
18 (E)-4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl oxime)-2-  
19 naphthalenyl)ethenyl]-benzoic acid (Compound A4) 90 mg (0.21  
20 mmol) of ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-  
21 (methoxymethoxy)-naphth-7-yl]naphth-2-oate (Compound B8) was  
22 converted into the title compound (white solid).

23 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 300 MHz): δ 1.26 (s, 3 H), 1.34 (s, 3 H), 1.59  
24 (m, 1 H), 1.98 (m, 3 H), 3.34 (s, 3 H), 4.68 (t, *J* = 4.5 Hz, 1 H), 4.78  
25 (d, *J* = 6.8 Hz, 1 H), 4.84 (d, *J* = 6.8 Hz, 1 H), 7.54 (d, *J* = 8.3 Hz,  
26 1 H), 7.70 (s, 1 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.90 (d *J* = 8.7 Hz, 1 H),  
27 8.00 (d, *J* = 8.7 Hz, 1 H), 8.09 (d, *J* = 8.7 Hz, 1 H), 8.21 (d, *J* = 8.7 Hz,  
28 1 H), 8.24(s, 1-H) , 8.63 (s, 1 H).

29 Ethyl-6-[5,6,7,8-tetrahydro-5,5-dimethyl-8-(O-acetyl)-naphth-7-yl]naphth-  
30 2-oate

31 (Compound B10)

1 To a cold (0 °C) solution of 61 mg (0.16 mmol) of ethyl-6-[5,6,7,8-  
2 tetrahydro-5,5-dimethyl-8-hydroxy)-naphth-7-yl]naphth-2-oate  
3 (**Compound B4**) in 2.0 mL of methylene chloride stirring under argon  
4 at 0°C was added successively, 76 mg (0.10 mL, 0.72 mmol) of  
5 triethylamine, 0.22 g (0.20 mL, 2.8 mmol) of acetylchloride and 7 mg  
6 (0.06 mmol) of 4-dimethylaminopyridine. The reaction was stirred at  
7 room temperature for 90 h, diluted with water, and extracted with  
8 CH<sub>2</sub>Cl<sub>2</sub> (2 x). The combined organic layer was washed with brine, dried  
9 over MgSO<sub>4</sub>, and concentrated *in vacuo*. The title compound was  
10 obtained as an oil after flash chromatography using silica, 10 % ethyl  
11 acetate in hexane.

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.31 (s, 3 H), 1.43 (s, 3 H), 1.46 (t,  
13 3 H, *J* = 7.1 Hz), 1.67-1.72 (m, 1 H), 1.94-2.12 (m, 3 H), 2.12 (s, 3  
14 H), 4.46 (q, *J* = 7.1 Hz, 2H), 6.06 (t, *J* = 4.4 Hz, 1 H), 7.51 (d, *J* =  
15 8.2 Hz, 1 H), 7.61 (d, *J* = 2.0 Hz, 1 H), 7.67 (dd, *J* = 2.0, 8.2 Hz, 1  
16 H), 7.78 (dd *J* = 1.7, 8.6 Hz, 1 H), 7.93 (d, *J* = 8.6 Hz, 1 H), 8.01 (d,  
17 *J* = 8.7 Hz, 1 H), 8.04 (s, 1 H), 8.09 (dd, *J* = 1.7, 8.7 Hz, 1 H), 8.62  
18 (s, 1 H).

19 Ethyl -6-[5,5-dimethyl-5,6-dihydro--naphthalen-8(7H)-anti-(O-methyl-  
20 oxime)-2yl]-naphthalen-2-oate (**Compound B11**)

21 A solution of 29 mg (0.08 mmol) of ethyl-6-[5,5-dimethyl-5,6-  
22 dihydro-naphthalen-8(7H) -one-2-yl]-naphthalen-2-oate (**Compound**  
23 **B6**), 27 mg (0.32 mmol) of methoxylamine hydrochloride and 68 mg  
24 (0.5 mmol) of sodium acetate in 2.0 mL of EtOH and 0.5 mL of  
25 tetrahydrofuran was heated at 50 °C for 18 h. An additional 27 mg of  
26 methoxylamine hydrochloride was added and the mixture refluxed for  
27 another 2 h. The mixture was concentrated *in vacuo*. The residue  
28 was diluted with water and extracted with EtOAc (2 x). The combined  
29 organic layer was dried over MgSO<sub>4</sub>, and concentrated *in vacuo*.  
30 Flash chromatography (silica, 5 % ethyl acetate in hexanes) of the  
31 crude material afforded the title compound as a solid.



1  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  1.35 (s, 6 H), 1.46 (t,  $J = 7.1$  Hz, 3  
2 H), 1.77 (t,  $J = 6.9$  Hz, 2 H), 2.84 (t,  $J = 6.9$  Hz, 2 H), 4.04 (s, 3H),  
3 4.45 (q,  $J = 7.1$  Hz, 2H), 7.47 (d,  $J = 8.2$  Hz, 1 H), 7.67 (dd,  $J = 2.1$ ,  
4 8.2 Hz, 1 H), 7.83 (dd,  $J = 1.8$ , 8.5 Hz, 1 H), 7.94 (d,  $J = 8.6$  Hz, 1 H),  
5 8.02 (d,  $J = 8.6$  Hz, 1 H), 8.07-8.10 (m, 2 H), 8.34 (d,  $J = 2.1$  Hz, 1  
6 H), 8.63 (s, 1 H).

7 6-[5,5-Dimethyl-5,6-dihydro--naphthlen-8(7H)-anti-(O-methyl-oxime)-2-  
8 yl]-2-naphthoic acid (Compound B12)

9 Employing the same general procedure as for the preparation of (E)-  
10 4-[2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-anti-(O-methyl oxime)-2-  
11 naphthalenyl)ethenyl]-benzoic acid (Compound A4) 22 mg (0.06 mmol)  
12 of ethyl-6-[5,5-dimethyl-5,6-dihydro--naphthlen-8(7H)-anti-(O-methyl-  
13 oxime)-2-yl]-naphthalen-2-oate (Compound B11) was converted into  
14 the title compound (white solid).

15  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 300 MHz):  $\delta$  1.30 (s, 6 H), 1.72 (t,  $J = 6.9$   
16 Hz, 3 H), 2.78 (t,  $J = 6.9$  Hz, 2 H), 3.97 (s, 3 H), 7.59 (d,  $J = 8.2$   
17 Hz, 1 H), 7.81 (dd,  $J = 2.1$ , 8.2 Hz, 1 H), 7.89 (dd,  $J = 1.8$ , 8.7 Hz, 1  
18 H), 8.00 (dd,  $J = 1.7$ , 8.6 Hz, 1 H), 8.12 (d,  $J = 8.7$  Hz, 1 H), 8.21-  
19 8.26 (m, 3 H), 8.64 (s, 1 H).

20 (5,6,7,8-Tetrahydro-5,5-dimethylnaphth-2-yl)boronic acid  
21 (Compound B13)

22 To a cold ( $-78^\circ\text{C}$ ) solution of 2.02 g (8.4 mmol) of 6-bromo-  
23 1,2,3,4-tetrahydro-1,1-dimethylnaphthalene in 11.0 mL of toluene,  
24 was added 4.6 g (6.8 mL, 10.9 mmol, 1.6 M in hexane) of n-BuLi.  
25 The resulting solution was stirred at  $-78^\circ\text{C}$  for 45 min. and then 2.40  
26 g (3.0 mL, 12.7 mmol) of triisopropylborate was dropwise added and  
27 the reaction stirred at room temperature for 12 h. The reaction was  
28 then diluted with 10% HCl, and extracted with ether (2 x). The  
29 combined organic layer was washed with brine, dried over  $\text{MgSO}_4$ ,  
30 and concentrated *in vacuo* to give an oil. Recrystallization from  
31 hexane afforded the title compound as a white solid.

1 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.34 (s, 6 H), 1.71 (m, 2 H), 87 (m,  
2 2 H), 1.89 (t, *J* = 6.3 Hz, 2 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.89 (s,  
3 1 H), 7.99 (d, *J* = 7.8 Hz, 1 H).

4 (5,5-Dimethyl-8-(*t*-butyldimethylsilyloxy)-5,6,7,8-tetrahydro-naphth-2-  
5 yl)boronic acid (Compound B14)

6 Employing the same general procedure as for the preparation of  
7 1,2,3,4-tetrahydro-1,1-dimethylnaphthyl-6-boronic acid (Compound  
8 B13) 12.40 g (34 mmol) of 6-bromo-1,2,3,4-tetrahydro-1,1-dimethyl-  
9 4-(*t*-butyldimethylsilyloxy)naphthalene (Compound B15) was  
10 converted into the title compound using 18.4 g (27.0 mL, 43 mmol,  
11 1.6 M in hexane) of *n*-BuLi and 9.37 g (11.50 mL, 50 mmol) of  
12 trisopropylborate.

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 0.22 (s, 3 H), 0.28 (s, 3 H), 0.98 (s,  
14 9 H), 1.33 (s, 3 H), 1.38 (s, 3 H), 1.62-2.09 (m, 4 H), 4.87 (m, 1  
15 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 8.07 (d, *J* = 7.8 Hz, 1 H), 8.29 (s, 1  
16 H).

17 2-(5,6,7,8-tetrahydro-5,5-dimethyl-8-(*t*-  
18 butyldimethylsilyloxy)naphthyl)bromide (Compound B15)

19 To a solution of 10.61 g (42 mmol) of 6-bromo-1,2,3,4-tetrahydro-  
20 1,1-dimethyl-4-hydroxynaphthalene in 100 mL of methylene chloride  
21 stirring at 0°C under argon, was added 5.23 g (7.20 mL, 52 mmol) of  
22 triethylamine, 0.55 g (4.5 mmol) of 4-dimethylaminopyridine, and  
23 7.71 g (51 mmol) of *t*-butyldimethylsilyl chloride consecutively. The  
24 resulting solution was stirred at 0°C to room temperature for 90 hours.  
25 The reaction was then diluted with water, and extracted with  
26 methylene chloride (2 x), the organic layers dried over Na<sub>2</sub>SO<sub>4</sub>, and  
27 concentrated *in vacuo* to give an oil. Purification was done using  
28 flash chromatography (silica, 4% ethyl acetate in hexane) to give the  
29 title compound as an oil.

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 0.15 (s, 3H), 0.18 (s, 3H), 0.95 (s,  
31 9H), 1.25 (s, 3H), 1.26 (s, 3H), 1.61-2.03 (m, 4H), 4.67 (m, 1H), 7.13

1 (d, J = 8.5 Hz, 1H), 7.30 (dd, J = 2.1, 8.5 Hz, 1H), 7.51 (d, J = 2.1  
2 Hz, 1H).

3 4,4-Dimethyl-7-acetyl-3,4-dihydronaphthalen-1(2H)-one (**Compound**  
4 **C1**)

5 A solution of 4,4-dimethyl-7-bromo-3,4-dihydronaphthalen-  
6 1(2H)one (**Compound G**) (1.78 g, 7 mmol), 1-ethoxyvinyltributyltin  
7 (EVTB) (3.3 g, 9.12 mmol),  
8 bis(triphenylphosphine)palladium(II)chloride (260 mg, 0.23 mmol) in  
9 THF (25 mL) was refluxed for 24 h under argon atmosphere. To the  
10 reaction, additional EVTB (1.5 g, 4.1 mmol) and  
11 bis(triphenylphosphine)palladium(II)chloride (200 mg, 0.2 mmol)  
12 were added and the mixture was and refluxed for an additional 24 h.  
13 The reaction mixture was cooled to room temperature and 10%  
14 hydrochloric acid (10 ml) was added. After 10 min, the mixture was  
15 extracted with ether (3 X 50 mL), the combined organic layer was  
16 washed with water (10 mL), 10% sodiumbicarbonate (10 mL), brine  
17 (10 mL), dried with magnesium sulfate. Solvent was removed under  
18 reduced pressure, and after purification by flash chromatography the  
19 title compound was obtained as a white solid.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.38 (s, 6H), 2.02 (t, J = 6.54 Hz, 2H), 2.73 (t,  
21 J = 6.54 Hz, 2H), 7.31 (d, J = 8.43 Hz, 1H), 7.63 (dd, J = 2.20, 8.43  
22 Hz, 1H), 8.13 (d, J = 2.20 Hz, 1H).

23 Ethyl 3-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]but-2(E)-  
24 enoate (**Compound C2**)

25 To a cold (-78 °C) slurry of sodiumhydride (336 mg, 14 mmol)  
26 in THF (10 mL) was added triethylphosphonoacetate (3.58 g, 16  
27 mmol). Cooling was discontinued and the mixture was stirred at  
28 ambient temperature. After 30 min, a solution of 4,4-dimethyl-7-  
29 acetyl-1,2,3,4-tetrahydronaphthalen-1(2H)-one (**Compound C1**, 800  
30 mg, 3.7 mmol) in THF (4 mL) was added and stirred for 36 h. The  
31 reaction mixture was diluted with ether (120 mL), and washed with

1 water (10 mL), brine (10 mL), dried with magnesium sulfate. Solvent  
2 was removed under reduced pressure, chromatographic purification  
3 gave the title compound as a colorless oil.

4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.33 (t,  $J = 7.1$  Hz, 3H), 1.41 (s, 6H), 2.04 (t,  $J$   
5 = 7.0 Hz, 2H), 2.59 (s, 3H), 2.76 (t,  $J = 7.0$  Hz, 2H), 4.23 (q,  $J = 7.1$   
6 Hz, 2H), 6.19 (s, 1H), 7.44 (d,  $J = 8.3$  Hz, 1H), 7.65 (dd,  $J = 2.0, 8.3$   
7 Hz, 1H), 8.15 (d,  $J = 2.0$  Hz, 1H).

8 3-[1-Hydroxy-4,4-dimethyl-1,2,3,4,-tetrahydronaphthalen-7-yl]but-  
9 2(E)-en-1-ol (Compound C3)

10 To a cold ( $-78^\circ\text{C}$ ) solution of ethyl 3-[4,4-dimethyl-1,2,3,4,-  
11 tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-enoate (Compound C2,  
12 2.7 g, 9.4 mmol) in methylenechloride (20 mL) was added  
13 diisobutylaluminum hydride (DibAl-H, 1M solution in  
14 methylenechloride) (45 mL). The reaction was gradually warmed to -  
15  $10^\circ\text{C}$ . The reaction was quenched by adding methanol (3 mL), water  
16 (10 mL), 10% hydrochloric acid (40 mL) and stirred for 10 min. The  
17 mixture was extracted with methylenechloride (3 x 50 mL). The  
18 combined organic layer was washed with water (10 mL), 10%  
19 sodiumbicarbonate (10 mL), brine (10 mL), dried with magnesium  
20 sulfate. Solvent was removed under reduced pressure to obtain the  
21 title compound as a white solid.

22  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.24 (s, 3H), 1.31 (s, 3H), 1.57-1.70 (m, 2H),  
23 1.82-1.96 (m, 2H), 2.03 (s, 3H), 4.29 (d,  $J = 6.6$  Hz, 2H), 4.68 (brs,  
24 1H), 5.95 (t,  $J = 6.6$  Hz, 1H), 7.28 (brs, 2H), 7.48 (s, 1H).

25 3-[4,4-Dimethyl-3,4,-dihydronaphthalen-1(2H)one-7-yl]but-2(E)-en-al  
26 (Compound C4)

27 To a solution of 3-[1-hydroxy-4,4-dimethyl-1,2,3,4,-  
28 tetrahydronaphthalen-7-yl]but-2(E)-en-1-ol (Compound C3, 1.5 g,  
29 6.1 mmol) in dichloromethane (35 mL) was added manganese dioxide  
30 (9 g, 106 mmol) in two portions and stirred at room temperature for  
31 48 h. After filtering out the manganese dioxide and removing the

- 1 solvent under reduced pressure the product was isolated as a white  
2 solid.  
3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.41 (s, 6H), 2.03 (t,  $J = 6.4$  Hz, 2H), 2.58 (s,  
4 3H), 2.75 (t,  $J = 6.4$  Hz, 2H), 6.41 (d,  $J = 7.7$  Hz, 1H), 7.48 (d,  $J =$   
5 8.31, 1H), 7.71 (dd,  $J = 2.2, 8.31$  Hz, 1H), 8.20 (d,  $J = 2.2$  Hz), 10.18  
6 (d,  $J = 7.7$  Hz, 1H).

1 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)one-7-yl]-3,7-  
2 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C5)

3 To a cold (-78 °C) solution of diethyl-(E)-3-ethoxycarbonyl-2-  
4 methylallylphosphonate in THF was added n-BuLi (1.6 mmol solution  
5 in hexanes, 2.2 mL, 3.5 mmol) followed by 3-[4,4-dimethyl-1,2,3,4,-  
6 tetrahydronaphthalen-1(2H)one-7-yl]but-2(E)-en-al (**Compound C4**,  
7 300 mg, 1.24 mmol) in THF (2 mL). The mixture was stirred for 16  
8 h at -78 °C. The mixture was treated with water and extracted with  
9 ether (3 X 40 mL). The combined organic layer was washed with  
10 water (10 mL), brine (10 mL) and dried with MgSO<sub>4</sub>. Solvent was  
11 removed under reduced pressure, the crude product was purified by  
12 column chromatography, followed by HPLC to give the title  
13 compound as a solid.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.30 (t, J = 7.1 Hz, 3H), 1.40 (s, 6H), 2.03 (t, J  
15 = 6.8 Hz, 2H), 2.26 (s, 3H), 2.38 (s, 3H), 2.75 (t, J = 6.8 Hz, 2H),  
16 4.20 (q, J = 7.1 Hz, 2H), 5.82 (s, 1H), 6.41 (s, J = 15.0 Hz, 1H), 6.64  
17 (d, J = 11.0 Hz, 1H), 7.01 (dd, J = 11.0, 15.0 Hz, 1H), 7.41 (d, J =  
18 8.2 Hz, 1H), 7.66 (dd, J = 2.0, 8.2 Hz, 1H), 8.14 (d, J = 2.0 Hz).

19 4,4-Dimethyl-7-acetyl-1-phenylthio-3,4-dihydronaphthalene  
20 (**Compound C7**)

21 Employing the procedure used for the preparation of 4,4-dimethyl-  
22 7-acetyl-3,4-dihydronaphthalen-1(2H)-one (**Compound C1**) 1.2 g,  
23 (3.5 mmol) of 4,4-dimethyl-7-Bromo-1-phenylthio-3,4-  
24 dihydronaphthalene (**Compound A35**) was converted to the title  
25 compound.

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.35 (s, 6H), 2.42 (d, J = 4.8 Hz, 2H), 2.43 (s,  
27 3H), 6.59 (t, J = 4.8 Hz, 1H), 7.10-7.27 (m, 4H), 7.32 (d, J = 8.5 Hz,  
28 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 1.9, 8.1 Hz, 1H), 8.18 (d,  
29 J = 1.9 Hz, 1H).

30 3-[4,4-Dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-2-en(E)-  
31 nitrile (Compound C8)

1        Employing the procedure used for the preparation of ethyl 3-[4,4-  
2        dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]but-2(E)-enoate  
3        (**Compound C2**) instead using diethylcyanomethylphosphonate (1.77  
4        g, 10 mmol), sodium hydride (220 mg, 9 mmol) and 4,4-dimethyl-7-  
5        acetyl-1-phenylthio-3,4-dihydronaphthalene (**Compound C7**, 924 mg,  
6        3 mmol) was converted to the title compound.  
7         $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.34 (s, 6H), 2.30 (s, 3H), 2.42 (d,  $J = 4.6$  Hz,  
8        2H), 5.38 (s, 1H), 6.61 (t,  $J = 4.6$  Hz, 1H), 7.10-7.37 (m, 7H), 7.69  
9        (d,  $J = 1.9$  Hz, 1H).

1 3-[4,4-Dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-yl]but-2-en(E)-  
2 aldehyde (Compound C9)

3 To a cold (-78 °C) solution of 3-[4,4-dimethyl-1-phenylthio-3,4-  
4 dihydronaphthalen-7-yl]but-2-en(E)-nitrile (**Compound C8**, 400 mg,  
5 1.2 mmol), in dichloromethane (10 mL) was added  
6 diisobutylaluminum hydride (DiBAL-H) (1M solution in  
7 dichloromethane, 2.5 mL, 2.5 mmol). The reaction was warmed to -40  
8 °C gradually over a period of 1 h. Then the reaction was quenched  
9 by adding methanol (1.5 mL), diluted with ether : ethylacetate (1:1,  
10 100 mL), washed with 10% HCl (10 mL), water (10 mL), and brine  
11 (10 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was  
12 removed under reduced pressure. The title compound was obtained as  
13 a colorless oil after silicagel chromatography.

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.36 (s, 6H), 2.40 (d, J = 1.3 Hz, 3H), 2.42 (d,  
15 J = 4.7 Hz, 2H), 6.25 (dd, J = 1.3, 7.9 Hz, 1H), 6.60 (t, J = 4.7 Hz,  
16 1H), 7.10-7.43 (m, 7H), 7.81 (d, J = 1.9 Hz, 1H), 10.11 (d, J = 7.9  
17 Hz, 1H).

18 Ethyl 7-[4,4-dimethyl-1-(phenylthio)-3,4,-dihydronaphthalen-7-yl]-3,7-  
19 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C10)

20 Employing the procedure used for the preparation of ethyl 7-[4,4-  
21 dimethyl-3,4,-dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-hept-  
22 2(E), 4(E), 6(E)trienoate (**Compound C5**) instead using diethyl-(E)-3-  
23 ethoxycarbonyl-2-methylallylphosphonate (786 mg, 3 mmol), n-BuLi  
24 (2.8 mmol), 3-[4,4-dimethyl-1-phenylthio-3,4-dihydronaphthalen-7-  
25 yl]but-2-en(E)-aldehyde (**Compound C9**, 280 mg, 0.84 mmol) was  
26 converted to the title compound.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.32 (t, J = 7.1 Hz, 3H), 1.36 (s, 6H), 2.12 (s,  
28 3H), 2.38 (s, 3H), 2.41 (d, J = 4.7 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H),  
29 5.82 (s, 1H), 6.29 (d, J = 14.8 Hz, 1H), 6.33 (d, J = 9.9 Hz, 1H), 6.58  
30 (t, J = 4.7 Hz, 1H), 6.96 (dd, J = 9.9, 14.8 Hz, 1H), 7.12-7.38 (m,  
31 7H), 7.74 (d, J = 1.7 Hz, 1H).



1 Ethyl 7-[4,4-dimethyl-1-phenylsulfonyl-3,4,-dihydronaphthalen-7-yl]-

2 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C11a)

3 Ethyl 7-[4,4-dimethyl-1-phenylsulfoxide-3,4,-dihydronaphthalen-7-yl]-

4 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C11b)

5 To a cold (0 °C) solution of ethyl 7-[4,4-dimethyl-1-phenylthio-

6 3,4,-dihydronaphthalen-7-yl]-3,7-dimethyl-hept-2(E), 4(E),

7 6(E)trienoate (Compound C10, 44 mg, 0.1 mmol) in

8 dichloromethane (3 mL) was added m-chloroperoxybenzoic acid

9 (approximately 60% concentration, 30 mg, 0.1 mmol). The mixture

10 was stirred for 2 h at 0 °C, diluted with dichloromethane (40 mL) and

11 washed successively with 10% sodiumbicarbonate (5 mL), water (5

12 mL) and brine (5 mL). The organic layer was dried (MgSO<sub>4</sub>) and the

13 solvent was removed under reduced pressure. The title compounds

14 were obtained after separation of the mixture by silicagel

15 chromatography.

16 Ethyl 7-[4,4-dimethyl-1-phenylsulfonyl-3,4,-dihydronaphthalen-7-yl]-

17 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound 11a)

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.23 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H), 2.17 (s,

19 3H), 2.39 (s, 3H), 2.51 (d, J = 4.9 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H),

20 5.84 (s, 1H), 6.36 (d, J = 15.1 Hz, 1H), 6.41 (d, J = 13.0 Hz, 1H),

21 6.99 (dd, J = 12.0, 15.1 Hz, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.34 (dd,

22 J = 1.9, 8.2 Hz, 1H), 7.45-7.60 (m, 4H), 7.93-8.0 (m, 3H).

23 Ethyl 7-[4,4-dimethyl-1-phenylsulfoxide-3,4,-dihydronaphthalen-7-yl]-

24 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound 11b)

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.32 (s, 3H), 1.30 (s, 3H), 1.31 (t, J = 7.1 Hz,

26 3H), 2.15 (s, 3H), 2.38 (s, 3H), 2.50 (d, J = 4.6 Hz, 2H), 4.19 (q, J =

27 7.1 Hz, 2H), 5.84 (s, 1H), 6.36 (d, J = 15.0 Hz, 1H), 6.39 (d, J = 11.6

28 Hz, 1H), 6.90-7.04 (m, 2H), 7.24-7.32 (m, 2H), 7.41-7.50 (m 3H),

29 7.53 (d, J = 1.8 Hz, 1H), 7.74 (dd, J = 2.5, 8.0 Hz, 2H).

30 Ethyl 7-[4,4-dimethyl-1,2,3,4,-tetrahydronaphthalen-1-hydroxy-7-yl]-

31 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C13)

1 To cold (0 °C) solution of ethyl 7-[4,4-dimethyl-3,4,-  
2 dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
3 6(E)trienoate (**Compound C5**, 6 mg, 0.02 mmol) in ether (3 mL) was  
4 added  $\text{ZnBH}_4$  (0.5 M solution in ether, 0.5 mL). The mixture was  
5 stirred for 30 min. and quenched the with water, diluted with ether  
6 (30 mL). The organic layer was washed with water (5 mL), 10% HCl  
7 (5 mL), water (5 mL), 10%  $\text{NaHCO}_3$  (5 mL) and brine (5 mL). The  
8 organic layer was dried with  $\text{MgSO}_4$ , and the solvent was removed  
9 under reduced pressure to obtain the title compound as a white solid.  
10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.26 (s, 3H), 1.30 (t,  $J = 7.1$  Hz, 3H), 1.34 (s,  
11 3H), 1.58-1.70 (m, 1H), 1.82-1.95 (m, 2H), 2.05-2.15 (m, 1H), 2.25  
12 (s, 3H), 2.38 (s, 3H), 4.18 (q,  $J = 7.1\text{Hz}$ ), 4.75 (brs, 1H), 5.81 (s, 1H),  
13 6.37 (d,  $J = 15.1$  Hz, 1H), 6.60 (d,  $J = 11.2$  Hz, 1H), 7.02 (dd,  $J =$   
14 11.2, 15.1 Hz, 1H), 7.31 (d,  $J = 8.3$  Hz, 1H), 7.39 (dd,  $J = 2.1, 8.3$   
15 Hz, 1H).

1 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-  
2 trifluoromethylsulfonyloxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
3 6(E)trienoate (Compound C14)

4 To a cold (-78 °C) stirring solution of ethyl 7-[4,4-dimethyl-3,4,-  
5 dihydronaphthalen-1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
6 6(E)trienoate (Compound C5, 190 mg, 0.55 mmol), in THF (10 mL)  
7 was added sodium bis(trimethylsilyl)amide (1M solution in THF, 0.5  
8 mL, 0.5 mmol). After 20 min. 2-*N,N*-  
9 bis(trifluoromethylsulfonyl)amino-5-chloropyridine (216 mg, 0.6  
10 mmol) in THF (2 mL) was added, after another 20 min. the  
11 temperature was increased to -10 °C and the mixture was stirred at  
12 this temperature for another 20 min. The reaction was quenched by  
13 adding aqueous NH<sub>4</sub>Cl (10 mL), extracted with ether (3 X 30 mL).  
14 The combined organic layer was washed successively with water (10  
15 mL) and brine (10 mL), dried with MgSO<sub>4</sub>. The solvent was  
16 removed, and the resulting crude mixture was purified by silicagel  
17 chromatography and HPLC to afford the title compound as a white  
18 solid.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.31 (t, J = 7.1 Hz, 3H), 1.32 (s, 6H), 2.25 (s,  
20 3H), 2.39 (s, 3H), 2.43 (d, J = 4.9, 2H), 4.19 (q, J = 7.1 Hz, 2H),  
21 5.83 (s, 1H), 5.99 (t, J = 4.9 Hz, 1H), 6.40 (d, J = 15.0 Hz, 1H), 6.57  
22 (d, J = 11.3 Hz, 1H), 7.01 (dd, J = 11.3, 15.0 Hz, 1H), 7.30 (d, J =  
23 8.0 Hz, 1H), 7.46 (dd, J = 1.9, 8.0 Hz, 1H), 7.47 (d, J = 1.9 Hz, 1H).

24 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-(2-thienyl)-7-yl]-3,7-  
25 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C15)

26 To a cold (-78 °C) solution of thiophene (252 mg, 3 mmol) in  
27 THF (2 mL) was added t-BuLi (1.4 M solution in cyclohexane, 2 mL,  
28 2.8 mmol) and the mixture was warmed to -30 °C over a period of 30  
29 min. The mixture was recooled to -78 °C and a solution of zinc  
30 chloride (408 mg, 3 mmol) in THF (1 mL) was added to it. The white  
31 turbid mixture was warmed to ambient temperature and stirred for 30

1 min. This mixture was transferred to a flask containing ethyl 7-[4,4-  
2 dimethyl-3,4,-dihydronaphthalen-1-trifluoromethylsulfonyloxy-7-yl]-  
3 3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound C14**, 118  
4 mg, 0.25 mmol), palladium tetrakis(triphenylphosphine) (250 mg, 0.22  
5 mmol) and THF (1 mL). The reactants were heated to 50 °C for 3 h.  
6 and then the reaction was quenched by adding aqueous NH<sub>4</sub>Cl (10  
7 mL). The reaction mixture was extracted with ethylacetate (3 X 20  
8 mL). The combined organic layer was washed with water (10 mL)  
9 and brine (10 mL), dried with MgSO<sub>4</sub>. The solvent was removed  
10 under reduced pressure and the title compound was obtained as pale  
11 yellow solid after silicagel chromatography.

12 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.29 (t, J = 7.1 Hz), 1.33 (s, 6H), 2.18 (s, 3H),  
13 2.33 (d, J = 4.8 Hz, 2H), 2.36 (s, 3H), 4.17 (q, J = 7.1 Hz, 2H), 5.79  
14 (s, 1H), 6.21 (t, J = 4.8 Hz, 1H) 6.33 (d, J = 15.1 Hz, 1H), 6.48 (d, J  
15 = 11.5 Hz, 1H), 6.98 (dd, J = 11.5, 15.1 Hz, 1H), 7.08 (br d, J = 3.4  
16 Hz, 2H), 7.26-7.29 (m, 1H), 7.32-7.41 (m, 2H), 7.52 (d, J = 1.6 Hz,  
17 1H).

18 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-(anti)(O-methyl-  
19 oxime)-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (**Compound**  
20 **C16**)

21 To a solution of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-  
22 1(2H)one-7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate  
23 (**Compound C5**, 25 mg, 0.07 mmol) in ethanol (2 mL) and THF (2  
24 mL), was added sodium acetate trihydrate (103 mg, 0.75 mmol)  
25 followed by methoxylamine hydrochloride (42 mg, 0.5 mmol). The  
26 mixture was stirred at ambient temperature for 16 h and diluted with  
27 ether (60 mL). The ether layer was washed successively with 10%  
28 NaHCO<sub>3</sub> (5 mL), water (5 mL) and brine (10 mL). The organic layer  
29 was dried with MgSO<sub>4</sub> and the solvent was removed under reduced  
30 pressure. After purification by chromatography on silicagel the title  
31 compound was obtained as a white solid.

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1  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.29 (s, 6H), 1.30 (t,  $J = 7.1$  Hz, 3H), 1.72 (t,  $J$   
2 = 7.0 Hz, 2H), 2.27 (s, 3H), 2.39 (s, 3H), 2.80 (t,  $J = 7.0$  Hz, 2H),  
3 4.03 (s, 3H), 4.18 (q,  $J = 7.1$  Hz, 2H), 5.82 (s, 1H), 6.40 (d,  $J = 15.0$   
4 Hz, 1H), 6.60 (2,  $J = 11.0$  Hz, 1H), 7.03 (dd,  $J = 11.0, 15.0$  Hz, 1H),  
5 7.33 (d,  $J = 8.3$  Hz, 1H), 7.44 (dd,  $J = 2.1$  Hz, 8.3 Hz, 1H), 8.07 (d,  $J$   
6 = 2.1 Hz, 1H).

1 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-  
2 (anti)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
3 6(E)trienoate (Compound C17a)

4 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-  
5 (syn)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
6 6(E)trienoate (Compound C17b)

7 To a cold (-78 °C) slurry of sodium hydride (24 mg, 1 mmol) in  
8 THF (3 mL) was added triethylphosphonoacetate (300 mg, 1.4 mmol).  
9 The mixture was stirred for 30 min. at 0 °C. To this mixture a  
10 solution of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)one-7-  
11 yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)-trienoate (Compound C5, 50  
12 mg, 0.15 mmol) in THF (2 mL) was added and stirred at ambient  
13 temperature for 48 h. The reaction was quenched by adding water (5  
14 mL) and extracted with ethyl acetate (3 X 30 mL). The combined  
15 organic layer was washed with water (5 mL), brine (5 mL) and dried  
16 (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the  
17 title compounds were obtained after silicagel chromatography and  
18 HPLC separation.

19 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-  
20 (anti)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
21 6(E)trienoate (Compound 17a)

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.30 (s, 6H), 1.30 (t, J = 7.1 Hz, 3), 1.34 (t, J =  
23 7.1 Hz, 3H), 1.73 (t, J = 6.6 Hz, 2H), 2.26 (s, 3H), 2.38 (s, 3H), 3.24  
24 (t, J = 6.6 Hz, 2H), 4.13-4.28 (m, 4H), 5.82 (s, 1H), 6.31 (s, 1H),  
25 6.40 (d, J = 15.0 Hz, 1H), 6.57 (d, J = 11.5 Hz, 1H), 7.01 (dd, J =  
26 11.5, 15.0 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 1.9, 8.3  
27 Hz, 1H), 7.66 (d, J = 1.9 Hz, 1H).

28 Ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1(2H)-  
29 (syn)(carbethoxymethylenyl)-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
30 6(E)trienoate (Compound C17b)

31 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.25 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz,

1 3H), 1.32 (s, 6H), 1.83 (t, J = 6.5 Hz, 2H), 2.23 (s, 3H), 2.38 (s, 3H),  
2 2.54 (t, J = 6.5 Hz, 2H), 4.12-4.25 (m, 4H), 5.81 (s, 2H), 6.38 (d, J  
3 = 15.1 Hz, 1H), 6.57 (d, J = 11.0 Hz, 1H), 7.01 (dd, J = 11.0, 15.1  
4 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 1.9, 8.3 Hz, 1H),  
5 7.72 (d, J = 1.9 Hz, 1H).

6 7-[4,4-Dimethyl-1,2,3,4,-tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-  
7 dimethyl-hept-2(E), 4(E), 6(E)trienoic acid (Compound C19)

8 To a solution of ethyl 7-[4,4-dimethyl-1,2,3,4,-  
9 tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
10 6(E)trienoate (Compound C13, 35 mg, 0.1 mmol) in THF (3 mL)  
11 and methanol (1 mL), was added lithiumhydroxide (1M solution in  
12 water, 0.3 mL, 0.3 mmol) and warmed to 60 °C for 6 h. The  
13 reaction mixture was diluted with ether : ethylacetate (1:1, 40 mL),  
14 acidified with 10% aqueous HCl to pH 6. The organic layer was  
15 washed with water (5 mL), brine (5 mL) and dried (MgSO<sub>4</sub>), and the  
16 solvent was removed under reduced pressure. After purification by  
17 preparative TLC the title compound was obtained as a pale yellow  
18 solid.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.26 (s, 3H), 1.34 (s, 3H), 1.55-1.65 (m, 1H),  
20 1.70-2.10 (m, 3H), 2.27 (s, 3H), 2.40 (s, 3H), 4.77 (t, J = 5.6 Hz,  
21 1H), 5.84 (s, 1H), 6.41 (d, J = 15.1 Hz, 1H), 6.62 (d, J = 11.1 Hz,  
22 1H), 7.08 (dd, J = 11.1, 15.1 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.40  
23 (dd, J = 1.9, 8.3 Hz, 1H), 7.57 (d, J = 1.9 Hz, 1H).

24 7-[4,4-Dimethyl-3,4,-dihydronaphthalen-1-(2-thienyl)-7-yl]-3,7-  
25 dimethyl-hept-2(E), 4(E), 6(E)trienoic acid (Compound C20)

26 Employing the procedure used for the preparation of 7-[4,4-  
27 dimethyl-1,2,3,4,-tetrahydronaphthalen-1-hydroxy-7-yl]-3,7-dimethyl-  
28 hept-2(E), 4(E), 6(E)trienoic acid (Compound C19), 20 mg (0.05  
29 mmol) of ethyl 7-[4,4-dimethyl-3,4,-dihydronaphthalen-1-(2-thienyl)-  
30 7-yl]-3,7-dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C15)  
31 was converted to the title compound.

130

- 1  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ ) :  $\delta$  1.30 (s, 6H), 2.19 (s, 3H), 2.32 (d,  $J = 4.8$   
2 Hz, 2H), 2.35 (s, 3H), 5.84 (s, 1H), 6.22 (t,  $J = 4.8$  Hz, 1H), 6.47 (d,  
3  $J = 15.1$  Hz, 1H), 6.58 (d,  $J = 11.0$  Hz, 1H), 7.05-7.18 (m, 3H), 7.38-  
4 7.55 (m, 4H).



1 Ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1-cyano-7-yl]-3,7-  
2 dimethyl-hept-2(E), 4(E), 6(E)trienoate (Compound C21)

3 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1-  
4 trifluoromethylsulfonyloxy-7-yl]-3,7-dimethyl-hept-2(E), 4(E),  
5 6(E)trienoate (**Compound C14**, 87 mg, 0.18 mmol) in THF (10 mL)  
6 were added tetrakis(triphenylphosphine)palladium (10 mg, 0.01 mmol)  
7 and zinc cyanide (42 mg, 0.36 mmol). The mixture was heated to 50  
8 °C for 1h. Additional quantities of  
9 tetrakis(triphenylphosphine)palladium (10 mg, 0.01 mmol) and zinc  
10 cyanide (42 mg, 0.36 mmol) were added and the mixture heated to 50  
11 °C for another 1h. The reaction was quenched with water (5 mL),  
12 extracted with ethyl acetate (2 X 20 mL), and the combined organic  
13 layer was washed with water, followed by brine. The organic layer  
14 was dried (MgSO<sub>4</sub>) and solvent removed under reduced pressure.  
15 After silicagel chromatography the title compound was isolated as a  
16 solid .  
17 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.29 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H), 2.26 (s,  
18 3H), 2.39 (s, 3H), 2.41 (d, J = 4.8 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H),  
19 5.83 (s, 1H), 6.41 (d, J = 15.0 Hz, 1H), 6.61 (d, J = 11.0 Hz, 1H),  
20 6.87 (t, J = 4.8 Hz, 1H), 7.01 (dd, J = 11.0, 15.0 Hz, 1H), 7.32 (d, J  
21 = 8.2 Hz, 1H), 7.44 (dd, J = 2.0, 8.2 Hz, 1H), 7.57 (d, J = 2.0 Hz,  
22 1H).

1 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-(O-ethyl oxime)-naphth-  
2 7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound 22a)

3 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-  
4 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound  
5 C22b)

6 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-  
7 1(2H)one-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
8 (Compound C5, 128 mg, 0.4 mmol) in THF (10 mL) and ethanol  
9 (10 mL), was added O-ethylhydroxylamine hydrochloride (280 mg,  
10 2.8 mmol), sodium acetate trihydrate (600 mg, 4.4 mmol) and the  
11 mixture was stirred at ambient temperature for 80 h. The reaction  
12 mixture was diluted with ethyl acetate (50 mL) and washed with  
13 water (10 mL) and brine (50 mL). The organic phase was dried over  
14 MgSO<sub>4</sub> and then concentrated *in vacuo* to a yellow oil. Purification  
15 by column chromatography (silica, 10% EtOAc-hexane) followed by  
16 HPLC separation (partisil 10, 10% EtOAc-hexane) afforded the title  
17 compounds as white solid in the ratios of 1 (*syn*) : 7 (*anti*).

18 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-(O-ethyl oxime)-naphth-  
19 7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C22a)

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.27-1.39 (m, 12H), 1.88 (t, J = 6.3Hz, 2H),  
21 2.25 (s, 3H), 2.39 (s, 3H), 2.56 (t, J = 6.5Hz, 2H), 4.19 (m, 4H), 5.81  
22 (s, 1H), 6.34 (d, J = 15.0Hz, 1H), 6.57 (d, J = 11.0Hz, 1H), 7.03 (dd,  
23 J = 11.4, 15.0Hz, 1H), 7.36 (d, J = 8.4Hz, 1H), 7.46 (dd, J = 2.0,  
24 8.6Hz, 1H), 8.65 (d, J = 2.0Hz, 1H).

25 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-  
26 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound  
27 C22b)

28 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28-1.31 (m, 9H), 1.36 (t, J = 8.2Hz, 3H), 1.73  
29 (t, J = 6.9Hz, 2H) 2.27 (s, 3H), 2.40 (s, 3H), 2.82 (t, J = 6.9Hz, 2H),  
30 4.20 (q, J = 7.2Hz, 2H), 4.3 (q, J = 7.1Hz, 2H), 5.83 (s, 1H), 6.38  
31 (d, J = 15.1Hz, 1H), 6.59 (d, J = 11.0Hz, 1H), 7.03 (dd, J = 11.2,

1 15.1Hz, 1H), 7.32 (d, J = 8.3Hz, 1H), 7.42 (dd, J = 2.1, 8.2Hz, 1H),  
2 8.09 (d, J = 2.0Hz, 1H).

3 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-(O-ethyl oxime)-naphth-7-  
4 yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (**Compound C24**).

5 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*syn*-(O-  
6 ethyl oxime)-naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
7 (**Compound C22a**, 7.8 mg, 0.02 mmol) in THF (1 mL) and ethanol  
8 (1 mL), was added 1M lithium hydroxide (0.08 mL, 0.08 mmol) and  
9 the mixture was stirred at ambient temperature for 8 days. Thereafter  
10 the reaction mixture was diluted with Et<sub>2</sub>O : EtOAc (1:1, 10ml) and  
11 acidified with 10% HCl to pH 4. The organic layer was washed with  
12 water (5 mL), brine (10 ml), dried (MgSO<sub>4</sub>) and the solvent was  
13 removed under reduced pressure. Recrystallization from  
14 EtOAc/hexane gave the title compound as a pale yellow solid.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (s, 6H), 1.36 (t, J = 7.1Hz, 3H), 1.88(t, J =  
16 8.7Hz, 2H), 2.25 (s, 3H), 2.39 (s, 3H), 2.55 (t, J = 6.5Hz, 2H), 4.20  
17 (q, J = 7.0Hz, 2H), 5.84 (s, 1H), 6.36 (d, J = 15.0Hz, 1H), 6.58 (d, J  
18 = 11.0Hz, 1H), 7.03 (dd, J = 11.2, 15.1Hz, 1H), 7.36 (d, J = 8.4Hz,  
19 1H), 7.47 (dd, J = 2.0, 8.6Hz, 1H), 8.65 (d, J = 2.0Hz, 1H).

20  
21 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-naphth-7-  
22 yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (**Compound C25**)

23 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-  
24 ethyl oxime)-naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
25 (**Compound C22b**, 40 mg, 0.1 mmol) in THF (2 mL) and ethanol (2  
26 mL), was added 1M lithium hydroxide (2 mL, 2 mmol) and the  
27 mixture was stirred at ambient temperature for 3 days and thereafter at  
28 50° C for 8h. The reaction mixture was diluted with Et<sub>2</sub>O : EtOAc  
29 (1:1, 10ml), and then acidified with 10% HCl to pH 4. The organic  
30 layer was washed with water (5 mL), brine (10 ml), dried (MgSO<sub>4</sub>)  
31 and the solvent was removed under reduced pressure. Recrystallization

1 from EtOAc/hexane gave the title compound as a pale yellow solid.  
2 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 6H), 1.36 (t, J = 7.0Hz, 3H), 1.73 (t, J  
3 = 7.0Hz, 2H) 2.28 (s, 3H), 2.41 (s, 3H), 2.81 (t, J = 6.9Hz, 2H), 4.25  
4 (q, J = 7.1Hz, 2H), 5.86 (s, 1H), 6.41 (d, J = 15.0Hz, 1H), 6.60 (d, J  
5 = 11.4Hz, 1H), 7.03 (dd, J = 11.4, 15.1Hz, 1H), 7.32 (d, J = 8.4Hz,  
6 1H), 7.42 (dd, J = 2.1, 8.4Hz, 1H), 8.09 (d, J = 2.0Hz, 1H).  
7 (-/+)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-(O-methoxymethyl)-  
8 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound  
9 C26)

10 To a solution of (-/+ )ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-  
11 hydroxy -naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
12 (Compound C13, 67 mg, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) were added  
13 *N,N*-diisopropylethylamine (91 mg, 1.1 mmol) , chloromethyl methyl  
14 ether (294 mg, 2.3 mmol) and the mixture was stirred at ambient  
15 temperature for 12 h. Then the reaction mixture was diluted with  
16 water (5 mL) and Et<sub>2</sub>O (25 mL) and washed with water (10 mL) and  
17 brine (10 mL). The organic phase was dried over MgSO<sub>4</sub> and  
18 concentrated *in vacuo* to a yellow oil. Purification by flash column  
19 chromatography (silica, 10% EtOAc-hexane) followed by reverse  
20 phase HPLC separation (partisil 10 ODS-2, 5% H<sub>2</sub>O-AcCN) afforded  
21 the title compound as a pale yellow oil.

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 3H), 1.29 (t, J = 7.1Hz, 3H), 1.34 (s,  
23 3H), 1.55-1.60(m, 1H), 1.91-2.05 (m, 3H), 2.24 (s, 3H), 2.38 (s, 3H),  
24 3.48(s, 3H), 4.16 (q, J = 7.1Hz, 2H), 4.65 (t, J = 4.7Hz, 1H), 4.76(d,  
25 J = 7.0Hz,1H), 4.87(d, J = 7.0Hz, 1H), 5.80 (s, 1H), 6.33 (d, J =  
26 15.2Hz, 1H), 6.55 (d, J = 11.5Hz, 1H), 7.01 (dd, J = 11.1, 15.0Hz,  
27 1H), 7.31 (d, J = 8.3Hz, 1H), 7.37 (dd, J = 2.1, 8.4Hz, 1H), 7.43 (d, J  
28 = 2.1Hz, 1H).

29 (+/-) 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-(O-methoxymethyl)-naphth-  
30 7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (Compound  
31 C27)

1 Employing the same general procedure as for the preparation of 7-  
2 [4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-naphth-7-yl]3,7-  
3 dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (**Compound C25**), (-  
4 /+)ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-(O-methoxymethyl)-  
5 naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound**  
6 **C26**, 20 mg, 0.05 mmol) was converted into the title compound  
7 (white solid).

8  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.23 (s, 3H), 1.30 (s, 3H), 1.55-1.60 (m,  
9 1H), 1.89-1.97 (m, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 3.40 (s, 3H), 4.59  
10 (t,  $J = 3.9\text{Hz}$ , 1H), 4.72 (d,  $J = 6.9\text{Hz}$ , 1H), 4.81 (d,  $J = 7.0\text{Hz}$ , 1H),  
11 5.85 (s, 1H), 6.49 (d,  $J = 15.1\text{Hz}$ , 1H), 6.66 (d,  $J = 11.3\text{Hz}$ , 1H),  
12 7.12 (dd,  $J = 11.1, 15.1\text{Hz}$ , 1H), 7.36 (d,  $J = 8.3\text{Hz}$ , 1H), 7.43 (dd,  $J$   
13  $= 2.1, 8.3\text{Hz}$ , 1H), 7.49 (d,  $J = 2.0\text{Hz}$ , 1H).

14 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1-(trimethylsiloxy)-naphth-2-  
15 yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound C28**)

16 To a solution of ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-  
17 1(2H)one-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
18 (**Compound C5**, 114 mg, 0.33 mmol) in anhydrous THF (10 mL)  
19 was added sodium bis-(trimethylsilyl) amide (0.36 ml, 0.36 mmol) at  
20  $-78^\circ\text{C}$  under argon. The reaction was stirred at  $-78^\circ\text{C}$  for 20  
21 minutes. To this reaction solution was then added a solution of  
22 trimethylsilylchloride (70.8 mg, 0.65 mmol) in HMPA (0.1 mL) and  
23 anhydrous THF (5 mL) at  $-78^\circ\text{C}$ . The reaction was allowed to stir at  
24  $-78^\circ\text{C}$  for 2 h. Then the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (25  
25 mL) and washed with water (10 mL), brine (10 mL). The organic  
26 phase was dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to a yellow  
27 oil. The product was purified by flash column chromatography  
28 (silica, 10% EtOAc-hexane) to afford the title compound as a pale  
29 yellow oil.

30  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  0.26 (s, 9H), 1.23 (t,  $J = 7.1\text{Hz}$ , 3H), 1.26  
31 (s, 6H), 2.25 (m, 5H), 2.37 (m, 3H), 4.08 (q,  $J = 7.1\text{Hz}$ , 2H), 5.15 (t,

1 J = 4.6Hz, 1H), 5.83 (s, 1H), 6.48 (d, J = 15.1Hz, 1H), 6.65 (d, J =  
2 11.0Hz, 1H), 7.13 (dd, J = 11.1, 15.0Hz, 1H), 7.26 (d, J = 8.1Hz,  
3 1H), 7.40 (dd, J = 2.1, 8.1Hz, 1H), 7.60 (d, J = 2.1Hz, 1H).

4 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS)-  
5 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-2(E),4(E),6(E)-  
6 trienoate (Compound C29a)

7 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(SR)-  
8 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-2(E),4(E),6(E)-  
9 trienoate (Compound C29b)

10 To a solution of (-/+ )ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1-  
11 hydroxy -naphth-7-yl]3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate  
12 (Compound C13, 110 mg, 0.3 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 mL)  
13 was added 3,4-dihydro-2H-pyran (62 mg, 0.7 mmol) followed by  
14 pyridinium p-toluenesulfonate (10 mg, 0.04 mmol). The reaction  
15 mixture was stirred at ambient temperature for 24 h. The reaction  
16 mixture was diluted with Et<sub>2</sub>O (20 mL) and washed successively with  
17 saturated NaHCO<sub>3</sub> (10 mL), water (10 mL) and brine (10 mL). The  
18 organic phase was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a  
19 yellow oil. Purification by flash column chromatography (silica, 15%  
20 EtOAc-hexane) followed by reverse phase HPLC separation (partisil  
21 10 ODS-2, 5% H<sub>2</sub>O-AcCN) afforded the title compounds as pale  
22 yellow oils.

23 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS)-  
24 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-2(E),4(E),6(E)-  
25 trienoate (Compound C29a)

26 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25-1.31 (m, 9H), 1.52-2.03 (m, 10H), 2.24 (s,  
27 3H), 2.38 (s, 3H), 3.50-3.60 (m, 1H), 4.01-4.07 (m, 1H), 4.12 (q, J =  
28 7.1Hz, 2H), 4.77 (t, J = 4.5Hz, 1H), 4.94 (t, J = 3.5Hz, 1H), 5.80 (s,  
29 1H), 6.32 (d, J = 15.0Hz, 1H), 6.56 (d, J = 11.5Hz, 1H), 7.02 (dd, J  
30 = 11.1, 15.0Hz, 1H), 7.28 (d, J = 8.3Hz, 1H), 7.36 (dd, J = 2.1,  
31 8.3Hz, 1H), 7.62 (d, J = 2.0Hz, 1H).

1 (+/-)Ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(SR)-  
 2 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-2(E),4(E),6(E)-  
 3 trienoate (**Compound C29b**)  
 4 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25-1.32 (m, 9H), 1.52-2.08 (m, 10H), 2.45 (s,  
 5 3H), 2.38 (s, 3H), 3.54-3.61 (m, 1H), 3.97-4.03 (m, 1H), 4.14 (q, J =  
 6 7.1Hz, 2H), 4.68 (t, J = 5.0Hz, 1H), 4.87 (t, J = 4.4Hz, 1H), 5.81 (s,  
 7 1H), 6.34 (d, J = 15.2Hz, 1H), 6.54 (d, J = 11.0Hz, 1H), 7.01 (dd, J  
 8 = 11.2, 15.1Hz, 1H), 7.30-7.40 (m, 3H)

9 (+/-)7-[4,4-Dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS)-  
 10 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-2(E),4(E),6(E)-  
 11 trienoic acid (**Compound C31**)

12 Employing the same general procedure as for the preparation of 7-  
 13 [4,4-dimethyl-3,4-dihydro-1(2H)-*anti*-(O-ethyl oxime)-naphth-7-yl]3,7-  
 14 dimethyl-hepta-2(E),4(E),6(E)-trienoic acid (**Compound C25**), (+/-)  
 15 )ethyl 7-[4,4-dimethyl-1,2,3,4-tetrahydro-1(RS)-(2'(RS)-  
 16 tetrahydropyranoxy)-3,7-dimethyl--naphth-2-yl]hepta-2(E),4(E),6(E)-  
 17 trienoate (**Compound C29a**, 15 mg, 0.03 mmol) was converted into  
 18 the title compound (white solid).

19 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.24 (s, 3H) 1.29 (s, 3H), 1.52-2.03 (m,  
 20 10H), 2.26 (s, 3H), 2.37 (s, 3H), 3.56-3.61 (m, 1H), 3.99-4.03 (m,  
 21 1H), 4.70 (t, J = 4.5Hz, 1H), 4.91 (t, J = 3.7Hz, 1H), 5.80 (s, 1H),  
 22 6.49 (d, J = 15.0Hz, 1H), 6.66 (d, J = 11.3Hz, 1H), 7.13 (dd, J =  
 23 11.1, 15.0Hz, 1H), 7.34 (d, J = 8.3Hz, 1H), 7.42 (dd, J = 2.1, 8.3Hz,  
 24 1H), 7.63 (d, J = 2.0Hz, 1H).

25 7-Acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
 26 (**Compound C33**)

27 To a solution of 7-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-  
 28 4,4-dimethylnaphthalene (**Compound A37**, 698 mg, 2.5 mmol) in  
 29 anhydrous THF (15 mL) was added (1-ethoxyvinyl)tributyltin (1.8 g,  
 30 5 mmol) and bis(triphenylphosphine)palladium(II) chloride (20 mg).  
 31 The resultant mixture was refluxed under argon atmosphere for 24 h.

1 The reaction mixture was cooled to ambient temperature and  
2 quenched with 10% HCl(5 mL), stirred for 20 minutes and extracted  
3 with Et<sub>2</sub>O (3 x 20 mL). The organic layer was washed with water (10  
4 mL), saturated NaHCO<sub>3</sub> (10 mL), brine (10 mL) and dried over  
5 MgSO<sub>4</sub>. The crude material was purified by flash column  
6 chromatography (silica, 5% EtOAc-hexane) to afford the title  
7 compound as a colorless oil.

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25 (s, 6H), 1.60 (t, J = 6.9Hz, 2H), 1.84 (s,  
9 3H), 1.97 (s, 3H), 2.49 (t, J = 6.9Hz, 2H), 2.57 (s, 3H), 7.35 (d, J =  
10 8.3Hz, 1H), 7.73 (dd, J = 2.0, 8.2Hz, 1H), 7.85 (d, J = 1.9Hz, 1H).  
11 3-[1(2H)-(Propyliden-2-yl))-3,4-dihydro-4,4-dimethylnaphthalen-7-  
12 yl]but-2(E)-en-nitrile (Compound C34)

13 To a slurry of NaH (117 mg, 4.8 mmol) in anhydrous THF (10  
14 mL) was added a solution of ethylcyanomethylphosphonate (947 mg,  
15 5.4 mmol) in THF (2 mL) at -78 °C under argon atmosphere. The  
16 reaction was allowed to warm to ambient temperature and a solution  
17 of 7-acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
18 dimethylnaphthalene (Compound C33, 394 mg, 1.6 mmol) in 5 mL  
19 of THF was added dropwise. The resultant reaction was stirred for 16  
20 h at ambient temperature and quenched with water (5mL). After  
21 extraction with EtOAc (2 x 10 mL), the combined organic layer was  
22 dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was  
23 purified by flash column chromatography (silica, 5% EtOAc-hexane) to  
24 afford the title compound as a colorless oil.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 6H), 1.60 (t, J = 7.0Hz, 2H), 1.85 (s,  
26 3H), 1.96 (s, 3H), 2.45 (s, 3H), 2.49 (t, J = 6.8Hz, 2H), 5.59 (s, 1H),  
27 7.24-7.35 (m, 3H). 3-[1(2H)-(Propyliden-2-yl))-3,4-dihydro-4,4-  
28 dimethylnaphthalen-7-yl]but-2(E)-en-aldehyde (Compound C35)

29 To a solution of 3-[1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
30 dimethylnaphthalen-7-yl]but-2(E)-en-onitrile (Compound C34, 311  
31 mg, 1.2 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added a solution of



1 diisobutylaluminum hydride ( 1M in CH<sub>2</sub>Cl<sub>2</sub>) (2.8 ml, 2.8 mmol)  
2 dropwise at -78 °C, under argon atmosphere. The reaction was  
3 allowed to stir at -78 °C for 6 h. A mixture of H<sub>2</sub>O (10 ml) and  
4 CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added and the resultant gel was filtered. The  
5 filtrate was concentrated *in vacuo* to a yellow oil. Purification by flash  
6 column chromatography (silica, 10% EtOAc-hexane) afforded the title  
7 compound as a pale yellow oil.

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 6H), 1.62 (t, J = 7.0Hz, 2H), 1.86 (s,  
9 3H), 1.98 (s, 3H), 2.50 (t, J = 6.9Hz, 2H), 2.57 (s, 3H), 6.40 (d, J =  
10 9.3Hz, 1H), 7.35-7.39 (m, 2H), 7.45 (d, J = 1.9Hz, 1H), 10.17 (d, J  
11 = 7.9Hz, 1H).

12 Ethyl-7-[1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethyl-naphthalen-  
13 7-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C36)

14 Employing the same general procedure as for the preparation of  
15 ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]3,7-  
16 dimethyl-hepta-2(E),4(E),6(E)-trienoate (Compound C5), 3-[1(2H)-  
17 (propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalen-7-yl]but-2(E)-  
18 en-aldehyde (Compound C35, 178 mg, 0.6 mmol) was converted  
19 into the title compound (pale yellow thick syrup).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 6H), 1.27 (t, J = 7.0Hz, 3H), 1.60 (t, J  
21 = 6.9Hz, 2H), 1.84 (s, 3H), 1.98 (s, 3H), 2.24 (s, 3H), 2.37 (s, 3H),  
22 2.48 (t, J = 6.7Hz, 2H), 4.14 (q, J = 7.1Hz, 2H), 5.79 (s, 1H), 6.33  
23 (d, J = 14.9Hz, 1H), 6.54 (d, J = 10.9Hz, 1H), 6.98 (dd, J = 11.0,  
24 15.0Hz, 1H), 7.25-7.28 (m, 2H), 7.36 (s, 1H).

25 7-Bromo-1(2H)-(phenylbenzyliden-yl)-3,4-dihydro-4,4-  
26 dimethylnaphthalene (Compound C37)

27 Employing the same general procedure as for the preparation of 7-  
28 bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
29 (Compound A37), 7-bromo-3,4-dihydro-4,4-dimethylnaphthalen-  
30 1(2H)-one (Compound G, 1.0 g, 3.96 mmol) was converted into  
31 the title compound (white solid) using titanium trichloride (5 g, 32

1 mmol), lithium wire (0.7 g, 100 mmol) and benzophenone (800 mg,  
2 4.4 mmol).  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 6H), 1.66 (t, J = 6.6Hz, 2H), 2.52 (t, J =  
4 6.8Hz, 2H), 6.92 (d, J = 1.7Hz, 1H), 6.98-7.00 (m, 2H), 7.15-7.21 (m,  
5 6H), 7.25-7.36 (m, 4H).

6 7-Acetyl-1(2H)-(phenylbenzyliden-yl)-3,4-dihydro-4,4-  
7 dimethylnaphthalene (**Compound C38**)

8 Employing the same general procedure as for the preparation of 7-  
9 acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
10 (**Compound C33**), 7-bromo-1(2H)-(phenylbenzyliden-yl)-3,4-dihydro-  
11 4,4-dimethylnaphthalene (**Compound C37**, 255 mg, 0.63 mmol) was  
12 converted into the title compound (colorless oil) using (1-  
13 ethoxyvinyl)tributyltin (353 mg, 0.97 mmol) and  
14 bis(triphenylphosphine)palladium(II) chloride (20 mg).

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6H), 1.70 (t, J = 6.4Hz, 2H), 1.99 (s,  
16 3H), 2.57 (t, J = 6.7Hz, 2H), 7.01-7.04 (m, 2H), 7.12-7.45 (m, 10H),  
17 7.65 (dd, J = 1.9, 8.3Hz, 1H).

18 3-(1(2H)-(phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphth-7-yl)-  
19 but-2(E)-enonitrile (**Compound C39**)

20 Employing the same general procedure as for the preparation of 3-  
21 (1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthyl)but-2(E)-  
22 enonitrile (**Compound C34**), the 7-acetyl-1(2H)-(phenylbenzylidenyl)-  
23 3,4-dihydro-4,4-dimethylnaphthalene (**Compound 38**, 206 mg, 0.56  
24 mmol) was converted into the title compound (colorless oil) using 327  
25 mg (1.85 mmol) of ethylcyanomethylphosphonate and 40.3 mg (1.68  
26 mmol) of sodium hydride.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6H), 1.70 (t, J = 6.3Hz, 2H), 2.03 (s,  
28 3H), 2.57 (t, J = 6.8Hz, 2H), 4.88 (s, 1H), 7.01 (dd, J = 2.0, 7.3Hz,  
29 2H), 7.14-7.37 (m, 11H).

30 3-(1(2H)-(phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphth-7-yl)-  
31 but-2(E)-enaldehyde (**Compound C40**)

1 Employing the same general procedure as for the preparation of 3-  
2 (1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthyl)-but-2(E)-  
3 enaldehyde (**Compound C35**), 3-(1(2H)-(phenylbenzylidenyl)-3,4-  
4 dihydro-4,4-dimethylnaphth-7-yl)-but-2-enonitrile (**Compound C39**,  
5 156 mg, 0.40 mmol) was converted into the title compound (pale  
6 yellow solid) using 0.9 ml (0.88 mmol) of diisobutylaluminum  
7 hydride (1 M in CH<sub>2</sub>Cl<sub>2</sub>).

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.35 (s, 6H), 1.70 (t, J = 6.5Hz, 2H), 2.04 (s,  
9 3H), 2.57 (t, J = 6.7Hz, 2H), 5.88 (d, J = 7.7Hz, 1H), 7.02 (dd, J =  
10 1.5, 7.4Hz, 2H), 7.12-7.36 (m, 11H), 9.98 (d, J = 7.8Hz, 1H).  
11 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1(2H)-(phenylbenzylidenyl)-  
12 naphth-7-yl]-3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound**  
13 **C41**)

14 Employing the same general procedure as for the preparation of  
15 ethyl 7-[4,4-dimethyl-3,4-dihydronaphthalen-1(2H)one-7-yl]3,7-  
16 dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound C5**), 3-(1(2H)-  
17 (phenylbenzylidenyl)-3,4-dihydro-4,4-dimethylnaphth-7-yl)-but-2(E)-  
18 enaldehyde (**Compound C40**, 101 mg, 0.26 mmol) was converted  
19 into the title compound (pale yellow thick oil).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (t, J = 7.1Hz, 3H), 1.34 (s, 6H), 1.69 (t, J  
21 = 6.3Hz, 2H), 1.85 (s, 3H), 2.32 (s, 3H), 2.54 (t, J = 6.9Hz, 2H), 4.14  
22 (q, J = 7.1Hz, 2H), 5.74 (d, J = 8.7Hz, 1H), 5.77 (s, 1H), 6.15 (d, J =  
23 14.9Hz, 1H), 6.80 (dd, J = 11.2, 15.0Hz, 1H), 7.04-7.36 (m, 13H).

24 7-Bromo-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene  
25 (**Compound C42**)

26 In a flame dried round bottom flask 7-bromo-3,4-dihydro-4,4-  
27 dimethylnaphthalen-1(2H)-one (**Compound G**, 2.0 g, 7.93 mmol)  
28 was dissolved in anhydrous THF (50 ml) and 3,4,5,6-tetrahydro-  
29 2(H)-pyrimidinone (DMPU) (11.5 ml, 95.16 mmol) was added, under  
30 argon atmosphere. The reaction was then cooled to -20 °C and a  
31 solution of t-butyl magnesium chloride (16 ml, 31.7 mmol) (2 M in

1 Et<sub>2</sub>O) was added dropwise and stirred at -20 °C for 2 h and at  
2 ambient temperature for 1 h, under argon atmosphere. The reaction  
3 was quenched at 0 °C with saturated ammonium chloride solution (20  
4 ml) and extracted with EtOAc (2 x 50 ml). The combined extract was  
5 washed with water (20 ml), brine (20 ml) and dried over MgSO<sub>4</sub>. The  
6 solvent was evaporated under reduced pressure to afford a yellow oil.  
7 To this yellow oil were added MeOH (50 ml) and p-tolylsulfonic acid  
8 (100 mg). The resultant reaction solution was heated in an oil bath  
9 (60 °C) for 3 h. The reaction was cooled and quenched with water  
10 (20 ml), extracted with EtOAc (2 x 50 ml). The combined extract was  
11 washed with saturated NaHCO<sub>3</sub> (20 ml), water (20 ml), brine (20 ml),  
12 and dried over MgSO<sub>4</sub>. The solvent was concentrated *in vacuo* and  
13 the title compound was obtained as a colorless oil after purification by  
14 flash chromatography (silica, hexane).

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.17 (s, 6H), 1.32 (s, 9H), 2.10 (d, J = 5.0Hz,  
16 2H), 5.95 (t, J = 4.9Hz, 1H), 7.13 (d, J = 8.3Hz, 1H), 7.24 (dd, J =  
17 2.1, 8.3Hz, 1H), 7.74 (d, J = 2.0Hz, 1H).

18 7-Acetyl-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethylnaphthalene  
19 (Compound C43)

20 Employing the same general procedure as for the preparation of 7-  
21 acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene  
22 (Compound C33), 7-bromo-1-(1,1-dimethylethyl)-3,4-dihydro-4,4-  
23 dimethylnaphthalene (Compound C42, 539 mg, 1.84 mmol) was  
24 converted into the title compound (white solid), using (1-  
25 ethoxyvinyl)tributyltin ( 2.6 g, 7.36 mmol) and  
26 bis(triphenylphosphine)palladium(II) chloride (80 mg).

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25 (s, 6H), 1.39 (s, 9H), 2.16 (d, J = 4.9Hz,  
28 2H), 2.60 (s, 3H), 6.00 (t, J = 4.9Hz, 1H), 7.39 (d, J = 8.1Hz, 1H),  
29 7.75 (dd, J = 1.7, 8.0Hz, 1H), 8.29 (d, J = 1.8Hz, 1H).

30 3-[1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethyl-naphthyl]-2-but-  
31 2(E)-enonitrile (Compound C44)

1 Employing the same general procedure as for the preparation of 3-  
2 (1-propylidene)-1,2,3,4-tetrahydro-4,4-dimethylnaphthyl)but-2(E)-  
3 enonitrile (**Compound C34**), 7-acetyl-1-(1,1-dimethylethyl)-3,4-  
4 dihydro-4,4-dimethylnaphthalene (**Compound C43**, 326 mg, 1.26  
5 mmol) was converted into the title compound (white solid) using 742  
6 mg (4.19 mmol) of ethylcyanomethylphosphonate and 91 mg (3.80  
7 mmol) of sodium hydride.

8  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.22 (s, 6H), 1.36 (s, 9H), 2.14 (d,  $J = 4.9\text{Hz}$ ,  
9 2H), 2.47 (s, 3H), 5.58 (s, 1H), 6.00 (t,  $J = 4.9\text{Hz}$ , 1H), 7.26 (dd,  $J =$   
10 2.0, 8.2Hz, 1H), 7.32 (d,  $J = 8.1\text{Hz}$ , 1H), 7.73 (d,  $J = 1.9\text{Hz}$ , 1H).  
11 3-[1-(1,1-dimethylethyl)-3,4-dihydro-4,4-dimethyl-naphth-7-yl]-but-  
12 2(E)-enaldehyde (**Compound C45**)

13 Employing the same general procedure as for the preparation of 3-  
14 (1-propylidene)-1,2,3,4-tetrahydro-4,4-dimethylnaphthyl)but-2(E)-  
15 enaldehyde (**Compound C35**), (E)- 3-(1-(1,1-dimethylethyl)-3,4-  
16 dihydro-4,4-dimethylnaphthyl)but-2(E)-enonitrile (**Compound C45**,  
17 256 mg, 0.95 mmol) was converted into the title compound (pale  
18 yellow solid) using 2.8 ml (2.84 mmol) of diisobutylaluminum  
19 hydride (1M in  $\text{CH}_2\text{Cl}_2$ ).

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.25 (s, 6H), 1.30 (s, 9H), 2.16 (d,  $J = 5.0\text{Hz}$ ,  
21 2H), 2.60 (s, 3H), 6.01 (t,  $J = 4.9\text{Hz}$ , 1H), 6.41 (d,  $J = 7.8\text{Hz}$ , 1H),  
22 7.38 (m, 2H), 7.86 (s, 1H), 10.19 (d,  $J = 8.0\text{Hz}$ , 1H).  
23 Ethyl 7-[4,4-dimethyl-3,4-dihydro-1-(1,1-dimethylethyl)-naphth-7-yl]-  
24 3,7-dimethyl-hepta-2(E),4(E),6(E)-trienoate (**Compound C46**)

25 Employing the same general procedure as for the preparation of  
26 ethyl 3,7-dimethyl-7-[5,5-dimethyl-5,6,7,8-tetrahydro-8-oxo-naphth-2-  
27 yl]hepta-2(E),4(E),6(E)-trienoate (**Compound C5**, (E)- 3-[1-(1,1-  
28 dimethylethyl)-3,4-dihydro-4,4-dimethyl-naphthyl]-2-butene-1-  
29 aldehyde (**Compound C45**, 82.6 mg, 0.29 mmol) was converted  
30 into the title compound (pale yellow solid).

31  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.24 (s, 6H), 1.28 (t,  $J = 7.1\text{Hz}$ , 3H), 1.39 (s,

1 9H), 2.15 (d, J = 4.9Hz, 2H), 2.28 (s, 3H), 2.40 (s, 3H), 4.15 (q, J =  
2 7.1Hz, 2H), 5.83 (s, 1H), 5.97 (t, J = 4.9Hz, 1H), 6.36 (d, J = 15.2Hz,  
3 1H), 6.54 (d, J = 11.5Hz, 1H), 7.00 (dd, J = 11.1, 15.0Hz, 1H), 7.31  
4 (s, 2H), 7.78 (s, 1H).

5 (+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-8-carbethoxymethyl-5,6,7,8-  
6 tetrahydronaphth-2-yl)azo]benzoate (Compound D1)

7 To a refluxing solution of zinc dust (0.15 g, 20 mesh, activated  
8 prior to use by washing with 2% of hydrochloric acid, water, 95%  
9 ethanol, acetone and anhydrous ether, then dried in vacuum for  
10 several hours) in 6 ml of dry benzene was slowly added a mixture of  
11 bromo ethyl acetate (0.082 ml, 0.74 mmol) and ethyl 4-[(5,5-  
12 dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-yl)azo]benzoate  
13 (Compound D10, 0.13 g, 0.371 mmol) in 6 ml of dry benzene. The  
14 resulting mixture was refluxed for 2 h then cooled to room  
15 temperature. The precipitate was filtered through celite and the  
16 filtrate was washed with cold 15% sulfuric acid. The organic phase  
17 was washed with saturated sodium bicarbonate, brine, dried over  
18 Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a red oil. Purification by  
19 flash chromatography (silica gel, 30% ethyl acetate in hexane)  
20 afforded the title compound as a red oil.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (t, J = 7.14 Hz, 3H), 1.34 (3H, s), 1.37 (s,  
22 3H), 1.43 (t, J = 7.14 Hz, 3H), 1.81 (m, 2H), 2.12 (m, 2H), 2.90 (q, J  
23 = 7.14 Hz, 2H), 4.22 (q, J = 7.14 Hz, 2H), 4.42 (q, J = 7.14 Hz, 2H),  
24 7.46 (d, J = 8.43 Hz, 1H), 7.80 (dd, J = 2.07, 6.35 Hz, 1H), 7.91 (d, J  
25 = 8.55 Hz, 2H), 8.17 (d, J = 8.55 Hz, 2H), 8.20 (d, J = 2.20 Hz, 1H).

26 Ethyl 4-[(5,5-dimethyl-8(7H)-(carbethoxymethylidenevl)-5,6-  
27 dihydronaphthalen-2-yl)azo]benzoate (Compound D2a)

28 Ethyl 4-[(5,5-dimethyl-8-(carbethoxymethyl)-5,6-dihydronaphthalen-2-  
29 yl)azo]benzoate (Compound D2b)

30 A solution of (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-8-  
31 carbethoxymethyl-5,6,7,8-tetrahydronaphth-2-yl)azo]benzoate

1 (Compound D1, 108 mg, 0.25 mmol), DCC (55.9 mg, 0.271 mmol)  
2 and CuCl (36.6 mg, 0.37 mmol) in 8 ml of dry benzene was heated  
3 under reflux for 7 days. After cooling to room temperature, the solids  
4 were filtered out and the solution was extracted with ethyl acetate.  
5 The combined organic layer was washed with brine and dried over  
6 Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, the crude  
7 material was purified by flash chromatography (silicagel, 10 % ethyl  
8 acetate in hexane) to afford the pure title compounds as red oils.

9 Ethyl 4-[(5,5-dimethyl-8(7H)-(carbethoxymethylidenyl)-5,6-  
10 dihydronaphthalen-2-yl)azo]benzoate (Compound D2a)

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.35 (m, 9H), 1.44 (t, J = 7.14 Hz, 3H), 1.79 (t,  
12 J = 6.75 Hz, 2H), 3.29 (t, J = 6.59 Hz, 2H), 4.27 (q, J = 7.14 Hz,  
13 2H), 4.44 (q, J = 7.14 Hz, 2H), 6.47 (s, 1H), 7.55 (d, J = 8.42 Hz,  
14 1H), 7.97 (m, 3H), 8.22 (m, 3H).

15 Ethyl 4-[(5,5-dimethyl-8-(carbethoxymethyl)-5,6-dihydronaphthalen-2-  
16 yl)azo]benzoate (Compound D2b)

17 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.22 (t, J = 7.10 Hz, 3H), 1.35 (s, 6H), 1.44 (t, J  
18 = 7.14 Hz, 3H), 2.32 (d, J = 4.39 Hz, 2H), 3.56 (s 2H), 4.17 (q, J =  
19 7.14 Hz, 2H), 4.44 (q, J = 7.14 Hz, 2H), 6.20 (t, J = 4.45 Hz, 1H),  
20 7.48 (d, J = 8.80 Hz, 1H), 7.81 (m, 2H), 7.92 (d, J = 8.49 Hz, 2H),  
21 8.20 (d, J = 8.48 Hz, 2H).

22 Ethyl 4-[(8(7H)-anti-(O-methyl oxime)-5,5-dimethyl-5,6-  
23 dihydronaphthalen-2-yl)azo]benzoate (Compound D3)

24 A solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-naphthalen-  
25 8(7H)-one-2-yl)azo]benzoate (Compound D10, 0.13 g, 0.371 mmol)  
26 (40mg, 0.114 mmol), NaOAc (29.3 mg, 0.286 mmol) and methoxy  
27 amine hydrochloride (14.3 mg, 0.137 mmol) in 3 ml of EtOH and 2  
28 ml of THF was stirred at room temperature for two weeks. The  
29 solvent was distilled off and the residue was diluted with ethyl  
30 acetate. The solution was washed with NaHCO<sub>3</sub> (sat.), water, brine  
31 and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced

1 pressure, the residue was purified by flash chromatography to afford  
2 the title compound as a red solid (34.8 mg).  
3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 3H), 1.44 (t,  $J$  = 7.14 Hz, 3H), 1.78 (t,  $J$   
4 = 6.96 Hz, 2H), 2.83 (t,  $J$  = 6.90 Hz, 2H), 4.06 (s, 3H), 4.43 (q,  $J$  =  
5 7.14 Hz, 2H), 7.51 (d,  $J$  = 8.48 Hz, 1H), 7.82 (dd,  $J$  = 2.20, 6.35 Hz,  
6 1H), 7.96 (d,  $J$  = 8.55 Hz, 2H), 8.21 (d,  $J$  = 8.48 Hz, 2H), 8.56 (d,  $J$   
7 = 2.14 Hz, 1H).

8 4-[(8(7H)-*Anti*-(O-methyl oxime)-5,5-dimethyl-5,6-dihydronaphthalen-  
9 2-yl)azo]benzoic acid (Compound D4)

10 A solution of ethyl 4-[(8(7H)-*anti*-(O-methyl oxime)-5,5-  
11 dimethyl-5,6-dihydronaphthalen-2-yl)azo]benzoate (Compound D3,  
12 57.7 mg, 0.16 mmol) and 2 ml of aqueous NaOH (12%) in 4 ml of  
13 THF and 2 ml of EtOH was stirred overnight at room temperature.  
14 The reaction was acidified with 10% HCl (to pH 4 and extracted with  
15 EtOAc. The combined organic layer was washed with water and  
16 brine, and dried over  $\text{Na}_2\text{SO}_4$ . Solvent was removed under reduced  
17 pressure to afford the title compound as a red solid.  
18  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.35 (s, 3H), 1.78 (t,  $J$  = 6.96 Hz, 2H), 2.82  
19 (t,  $J$  = 6.90 Hz, 2H), 4.00 (s, 3H), 7.67 (d,  $J$  = 8.54 Hz, 1H), 7.90  
20 (dd,  $J$  = 2.20, 6.59 Hz, 1H), 8.03 (d,  $J$  = 8.66 Hz, 2H), 8.24 (d,  $J$  =  
21 8.48 Hz, 2H), 8.54 (d,  $J$  = 2.14 Hz, 1H).

22 (+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-  
23 yl)azo]benzoate (Compound D5)

24 To a solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-naphthalen-  
25 8(7H)-one-2-yl)azo]benzoate (Compound D10, 60 mg, 0.171 mmol)  
26 in 2 ml of THF and 7 ml of EtOH at 0 °C was added  $\text{NaBH}_4$  (6.5  
27 mg, 0.171 mmol) and the mixture stirred for 3 h. The reaction was  
28 quenched by slow addition of cold water. Solvent was removed under  
29 reduced pressure and the residue was extracted with ethyl acetate.  
30 The organic layer was washed with brine, dried ( $\text{MgSO}_4$ ) and solvent  
31 removed under reduced pressure. The crude product was purified by



1 flash chromatography (silica, ethyl acetate/hexane, 1 : 3) to afford the  
2 title compound as a red oil.

3 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 3H), 1.38 (s, 3H), 1.43 (t, J = 7.14 Hz,  
4 3H), 1.68 (m, 1H), 1.92 (m, 2H), 2.13 (m, 1H), 4.42 (q, J = 7.14 Hz,  
5 2H), 4.85 (m, 1H), 7.49 (d, J = 8.48 Hz, 1H), 7.85 (dd, J = 2.2, 6.29  
6 Hz, 1H), 7.94 (d, J = 8.61 Hz, 2H), 8.05 (d, J = 2.13 Hz, 1H), 8.20  
7 (d, J = 8.55 Hz, 2H).

8 (+/-) Ethyl 4-[(5,5-dimethyl-8-(methoxymethoxy)-5,6,7,8-  
9 tetrahydronaphthalen-2-yl)azo]benzoate (Compound D6)

10 To a solution of (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-  
11 tetrahydronaphthalen-2-yl)azo]benzoate (Compound D5, 49.7 mg,  
12 0.141 mmol) in 4 ml of dry CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was added isopropyl  
13 ethyl amine (0.152 ml, 0.847 mmol) followed by chloromethyl methyl  
14 ether (0.0323 ml, 0.423 mmol). The reaction mixture was stirred at  
15 room temperature for 12 h. Solvent was removed under reduced  
16 pressure, the residue was dissolved in ethyl acetate and the solution  
17 was washed with NaHCO<sub>3</sub> (sat.), and brine. The organic layer was  
18 dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure,  
19 the residue was purified by flash chromatography (silica, ethyl acetate :  
20 hexane, 1 : 3) to afford the title compound as a red oil.

21 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 3H), 1.39 (s, 3H), 1.43 (t, J = 7.08 Hz,  
22 3H), 1.64 (m, 1H), 2.07 (m, 3H), 3.52 (s, 3H), 4.43 (q, J = 7.08 Hz,  
23 2H), 4.75 (t, J = 5.06 Hz, 1H), 4.84 (d, J = 6.90 Hz, 1H), 4.93 (d, J =  
24 6.90 Hz, 1H), 7.50 (d, J = 8.43 Hz, 1H), 7.83 (dd, J = 2.19, 6.29 Hz,  
25 1H), 7.95 (m, 3H), 8.19 (d, J = 8.55 Hz, 2H).

26 (+/-) 4-[(5,5-Dimethyl-8-(methoxymethoxy)-5,6,7,8-  
27 tetrahydronaphthalen-2-yl)azo]benzoic acid (Compound D7)

28 Using the same procedure as for the preparation of 4-[(8(7H)-  
29 anti-(O-methyl oxime)-5,5-dimethyl-5,6-dihydronaphthalen-2-  
30 yl)azo]benzoic acid (Compound D4), (+/-) ethyl 4-[(5,5-dimethyl-8-  
31 (methoxymethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)azo]benzoate

1 (Compound D6, 34 mg, 0.093 mmol) was converted into the title  
2 compound (red solid).

3  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  132 (s, 3H), 1.37 (s, 3H), 1.63 (m, 1H), 1.99  
4 (m, 3H), 3.45 (s, 3H), 4.75 (t,  $J$  = 6.1 Hz, 1H), 4.80 (d,  $J$  = 6.96 Hz,  
5 1H), 4.89 (d,  $J$  = 6.96 Hz, 1H), 7.62 (d,  $J$  = 8.55 Hz, 1H), 7.84 (dd,  $J$   
6 = 2.19, 6.29 Hz, 1H), 8.00 (m, 3H), 8.22 (d,  $J$  = 8.55 Hz, 2H).

7 3,4-dihydro-4,4-dimethyl-7-nitro-naphthalen-1(2H)-one (Compound  
8 D8)

9 To 1.7 mL (3.0g, 30.6 mmol, 18M)  $\text{H}_2\text{SO}_4$  at  $-5^\circ\text{C}$  (ice-NaCl  
10 bath) was slowly added 783.0 mg (4.49 mmol) of 3,4-dihydro-4,4-  
11 dimethyl-naphthalen-1(2H)-one. A solution of  $\text{HNO}_3$  (426.7 mg 6.88  
12 mmol, 0.43 mL, 16M), and 1.31g (0.013 mol, 0.74 mL, 18 M) of  
13  $\text{H}_2\text{SO}_4$  were slowly added. After 20 min, ice was added and the  
14 resulting mixture was extracted with EtOAc. The combined extracts  
15 were concentrated under reduced pressure to give a yellow oil from  
16 which the title compound, a pale yellow solid, was isolated by  
17 column chromatography (10% EtOAc / hexanes).

18  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.83 (1H, d,  $J$  = 2.6 Hz), 8.31 (1H, dd,  $J$  =  
19 2.8, 8.9 Hz), 7.62 (1H, d,  $J$  = 8.7 Hz), 2.81 (2H, t,  $J$  = 6.5 Hz), 2.08  
20 (2H, t,  $J$  = 6.5 Hz), 1.45 (6H, s).

21 3,4-dihydro-4,4-dimethyl-7-amino-naphthalen-1(2H)-one (Compound  
22 D9)

23 A solution of 230.0 mg (1.05 mmol) 3,4-dihydro-4,4-dimethyl-  
24 7-nitro-naphthalen-1(2H)-one (Compound D8) in 5.0 mL of EtOAc  
25 was stirred at room temperature with a catalytic amount of 10% Pd-C  
26 under 1 atm of  $\text{H}_2$  for 24 h. The catalyst was removed by filtration  
27 through a pad of Celite, and the filtrate concentrated under reduced  
28 pressure to give the title compound as a dark green oil.

29  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.30 (1H, d,  $J$  = 2.7 Hz), 7.22 (1H, d,  $J$  = 8.4  
30 Hz), 6.88 (1H, dd,  $J$  = 2.7, 8.5 Hz), 2.70 (2H, t,  $J$  = 6.6 Hz), 1.97  
31 (2H, t,  $J$  = 6.6 Hz), 1.34 (6H, s).

1 Ethyl 4-[(5,6-dihydro-5,5-dimethyl-8(7H)-one-naphthalen-2-yl)azo]-  
2 benzoate (Compound D10)

3 To a solution of 198.7 mg (1.05 mmol) 3,4-dihydro-4,4-  
4 dimethyl-7-amino-naphthalen-1(2H)-one (Compound D9) in 5.0 mL  
5 glacial acetic acid was added 180.0 mg (1.00 mmol) of ethyl 4-  
6 nitrosobenzoate. The resulting solution was stirred overnight at room  
7 temperature, and then concentrated under reduced pressure. The  
8 product was isolated from the residual oil as a red solid, by column  
9 chromatography (15% EtOAc - hexanes).

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  8.57 (1H, d,  $J = 2.0$  Hz), 8.19 (2H, d,  $J = 8.4$   
11 Hz), 8.07 (1H, d,  $J = 8.0$  Hz), 7.94 (2H, d,  $J = 8.4$  Hz), 7.58 (1H, d,  $J$   
12  $= 8.6$  Hz), 4.41 (2H, q,  $J = 7.1$  Hz), 2.79 (2H, t,  $J = 6.6$  Hz), 2.07  
13 (2H, t,  $J = 7.02$  Hz), 1.44 (6H, s), 1.42 (3H, t,  $J = 7.1$  Hz).

14 Ethyl 4-[(5,6-dihydro-5,5-dimethyl-8-(trifluoromethylsulfonyl)oxy-  
15 naphthalen-2-yl)azo]-benzoate (Compound D11)

16 To a solution of 90.4 mg sodium bis(trimethylsilyl)amide (0.48  
17 mmol, 0.48 mL of a 1.0 M THF solution) in 2.0 mL THF at  $-78^\circ\text{C}$ ,  
18 was added 153.0 mg (0.437 mmol) of ethyl 4-[(5,6-dihydro-5,5-  
19 dimethyl-8(7H)-one-naphthalen-2-yl)azo]-benzoate (Compound D10)  
20 in 2.0 mL THF. The dark red solution was stirred at  $-78^\circ\text{C}$  for 30  
21 min and then 204.0 mg (0.520 mmol) 2-[*N,N*-  
22 bis(trifluoromethylsulfonyl)amino]-5-chloropyridine was added as a  
23 solution in 2.0 mL THF. The reaction mixture was allowed to warm  
24 to room temperature and after 3 h was quenched by the addition of  
25  $\text{H}_2\text{O}$ . The organic layer was concentrated to a red oil under reduced  
26 pressure. The product was isolated by column chromatography (25%  
27 EtOAc / hexanes) as a red oil.

28  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  8.21 (2H, d,  $J = 8.6$  Hz), 7.96 (2H, d,  $J = 8.6$   
29 Hz), 7.94 (2H, m), 7.49 (1H, d,  $J = 8.2$  Hz), 6.08 (1H, t,  $J = 2.5$  Hz),  
30 4.42 (2H, q,  $J = 7.1$  Hz), 2.49 (2H, d,  $J = 4.8$  Hz), 1.44 (3H, t,  $J =$   
31 7.1 Hz), 1.38 (6H, s).

1 Ethyl 4-[(5,5-dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-  
2 yl)azo]benzoate (Compound D12)

3 To a cold solution (-78 °C) of thiophene (0.07 ml, 0.75 mmol)  
4 in 1.5 ml of THF was added t-BuLi (0.457 ml, 0.75 mmol, 1.7 M in  
5 pentane) and stirred for 2 h. To this solution, ZnCl<sub>2</sub> (168 mg, 1.2  
6 mmol) in 1.5 ml of THF was added. The resulting solution was  
7 warmed to room temperature, stirred for 1h and was added (via  
8 cannula) to a solution of ethyl 4-[(5,6-dihydro-5,5-dimethyl-8-  
9 trifluoromethylsulfonyloxy-naphthalen-2-yl)azo]benzoate (Compound  
10 D11, 150 mg, 0.30 mmol) and  
11 tetrakis(triphenylphosphine)palladium(0) (10.6 mg) in 2.5 ml of THF.  
12 The resulting mixture was heated at 50 °C for 2.5 h. The reaction was  
13 diluted with sat. aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate. The  
14 combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to  
15 an oil. The crude product was purified by flash chromatography  
16 (silica, ethyl acetate : hexane 5 : 95) to afford the title compound as a  
17 red foam.

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.40 (s, 6H), 1.44 (t, J = 7.14 Hz, 3H), 2.41 (d,  
19 J = 4.82 Hz, 2H), 4.42 (q, J = 7.14 Hz, 2H), 6.29 (t, J = 4.83 Hz,  
20 1H), 7.14 (m, 2H), 7.32 (dd, J = 1.52, 3.36, 1H), 7.53 (d, J = 8.31  
21 Hz, 1H), 7.84 (dd, J = 2.08, 6.17 Hz, 1H), 7.92 (d, J = 8.60 Hz, 2H),  
22 8.03 (d, J = 2.07 Hz, 1H), 8.18 (d, J = 8.61 Hz, 2H).

23 4-[(5,5-Dimethyl-8-(2-thienyl)-5,6-dihydronaphthalen-2-yl)azo]benzoic  
24 acid (Compound D13)

25 Using the same procedure as for the preparation of 4-[(8(7H)-  
26 *anti*-(O-methyl oxime)-5,5-dimethyl-5,6-dihydronaphthalen-2-  
27 yl)azo]benzoic acid (Compound D4), ethyl 4-[(5,5-dimethyl-8-(2-  
28 thienyl)-5,6-dihydronaphthalen-2-yl)azo]benzoate (Compound 12, 100  
29 mg, 0.258 mmol) was converted into the title compound (red solid).

30 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.40 (s, 6H), 2.43 (d, J = 4.83 Hz, 2H), 2.82  
31 (b, 1H), 6.32 (t, J = 4.88 Hz, 1H), 7.19 (m, 2H), 7.50 (d, J = 4.88 Hz,

1 1H), 7.65 (d, J = 8.24 Hz, 1H), 7.95 (m, 4H), 8.21 (d, J = 8.55 Hz,  
2 2H).  
3 3,4-dihydro-4,4-dimethyl-7-acetyl-naphthalen-1(2H)-one (Compound  
4 D14a); and 3,4-dihydro-4,4-dimethyl-6-acetyl-naphthalen-1(2H)-one  
5 (Compound D14b)

6 To a cold (0° C) mixture of aluminum chloride (26.3 g, 199.0  
7 mmols) in dichloromethane (55 mL) were added acetylchloride (15 g,  
8 192 mmols) and 1,2,3,4-tetrahydro-1,1-dimethylnaphthalene (24.4g,  
9 152mmols) in dichloromethane (20 mL) over 20 minutes. The reaction  
10 mixture was warmed to ambient temperature and stirred for 4 h. Ice  
11 (200 g) was added to the reaction flask and the mixture diluted with  
12 ether (400 mL). The layers were separated and the organic phase was  
13 washed with 10% HCl (50 mL), water (50 mL), 10% aqueous sodium  
14 bicarbonate, and saturated aqueous NaCl (50 mL) and thereafter dried  
15 over MgSO<sub>4</sub>. The solvent was removed by distillation to afford a  
16 yellow oil which was dissolved in benzene (50 mL).

17 To a cold (0° C) solution of acetic acid (240 mL) and acetic  
18 anhydride (120 mL) was added chromiumtrioxide (50 g, 503 mmols)  
19 in small portions over 20 mins under argon. The mixture was stirred  
20 for 30 mins at 0° C and diluted with benzene (120 mL). The benzene  
21 solution prepared above, was added with stirring via an addition  
22 funnel over 20 mins. After 8 h, the reaction was quenched by the  
23 careful addition of isopropanol (50 mL) at 0° C, followed by water  
24 (100 mL). After 15 mins, the reaction mixture was diluted with ether  
25 (1100 mL) and water (200 mL), and then neutralized with solid  
26 sodium bicarbonate (200 g). The ether layer was washed with water  
27 (100 mL), and saturated aqueous NaCl (2 x 100 mL), and dried over  
28 MgSO<sub>4</sub>. Removal of the solvent under reduced pressure afforded a  
29 mixture of the isomeric diketones which were separated by  
30 chromatography ( 5% EtOAc / hexanes).  
31 (Compound D14a): <sup>1</sup>H NMR (CDCl<sub>3</sub>) : d 8.55 (1H, d, J = 2.0 Hz),

1 8.13 (1H, dd, J = 2.0, 8.3 Hz), 7.53 (1H, d, J = 8.3 Hz), 2.77 (2H, t,  
2 J = 6.6 Hz), 2.62 (3H, s), 2.05 (2H, t, J = 6.6 Hz), 1.41 (6H, s).

3 (**Compound D14b**):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : d 8.10 (1H, d, J = 8.1 Hz),  
4 8.02 (1H, d, J = 1.6 Hz), 7.82 (1H, dd, J = 1.6, 8.1 Hz), 2.77 (2H, t, J  
5 = 7.1 Hz), 2.64 (3H, s), 2.05 (2H, t, J = 7.1 Hz), 1.44 (6H, s).

6 6-(2-methyl-1,3-dioxolan-2-yl)-3,4-dihydro-4,4-dimethylnaphthalen-  
7 1(2H)-one (**Compound D15**)

8 A solution of 1.80 g (8.34 mmol) of a 1:5 mixture of 3,4-  
9 dihydro-4,4-dimethyl-7-acetyl-naphthalen-1(2H)-one (**Compound**  
10 **D14a**); and 3,4-dihydro-4,4-dimethyl-6-acetyl-naphthalen-1(2H)-one  
11 (**Compound D14b**) in 50 mL benzene was combined with 517.7 mg  
12 (8.34 mmol) of ethylene glycol and 20.0 mg (0.11 mmol) of *p*-  
13 toluenesulfonic acid monohydrate. The resulting solution was heated  
14 to reflux for 18 h, cooled to room temperature, and concentrated  
15 under reduced pressure. The title compound was isolated by column  
16 chromatography (10% EtOAc - hexanes) as a colorless oil.

17  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  8.01 (1H, d, J = 8.2 Hz), 7.51 (1H, s), 7.43  
18 (1H, dd, J = 1.7, 6.4 Hz), 4.07 (2H, m), 3.79 (2H, m), 2.74 (2H, t, J  
19 = 6.5 Hz), 2.04 (2H, t, J = 7.1 Hz), 1.67 (3H, s), 1.46 (6H, s).

20 (+/-) 6-(2-Methyl-1,3-dioxolan-2-yl)]-1,2,3,4-tetrahydro-4,4-dimethyl-  
21 1-hydroxy-

22 1-(carboethoxymethyl)-naphthlene (**Compound D16**)

23 Using the same procedure as for the preparation of ethyl 4-  
24 [(5,6,7,8-tetrahydro-5,5-dimethyl-8-hydroxy-8-  
25 (carboethoxymethyl)naphthalen-2-yl)azo]benzoate, 6-(2-methyl-1,3-  
26 dioxolan-2-yl)]-3,4-dihydro-4,4-dimethylnaphthalen-1(2H)-one  
27 (**Compound D1**), 6-(2-methyl-1,3-dioxolan-2-yl)-3,4-dihydro-4,4-  
28 dimethylnaphthalen-1(2H)-one (**Compound D15**, 300 mg, 1.15  
29 mmol) was converted to the title product (321 mg, light yellow oil),  
30 using zinc dust (0.5 g, pretreated) and bromo ethyl acetate (0.256 ml,  
31 0.30 mmol) in 10 ml of benzene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (t, J = 7.08 Hz, 3H), 1.30 (s, 3H), 1.32 (s, 3H), 1.65 (s, 3H), 2.06 (s, 2H), 2.80 (q, J = 1.45 Hz, 2H), 3.77 (m, 2H), 4.05 (m, 2H), 4.13 (q, J = 7.14 Hz, 2H), 4.22 (q, J = 7.14 Hz, 2H), 7.30 (dd, J = 1.71, 6.54 Hz, 1H), 7.42 (d, J = 1.77 Hz, 1H), 7.53 (d, J = 8.18 Hz, 1H).

3,4-Dihydro-4,4-dimethyl-1-(carboethoxymethyl)-6-acetyl-naphthalene  
(Compound D17)

A solution of (+/-) 6-(2-methyl-1,3-dioxolan-2-yl)-1,2,3,4-tetrahydro-4,4-dimethyl-1-hydroxy-1-(carboethoxymethyl)-naphthlene ((Compound D16, 321 mg, 0.90 mmol) and catalytic amount of TsOH in 20 ml of benzene was refluxed for 12 h. During the reaction the water generated from the reaction was periodically removed by a Dean-Stark trap. The solvent was removed and the residue was purified by column chromatography (silica, ethyl acetate/hexane (1/3)) to give the title compound as an oil (215 mg).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.20 (t, J = 7.14 Hz, 3H), 1.33 (s, 6H), 2.30 (d, J = 3.42 Hz, 2H), 2.60 (s, 3H), 3.50 (s, 2H), 4.16 (q, J = 7.14 Hz, 2H), 6.06 (t, J = 4.64 Hz, 1H), 7.28 (d, J = 2.80 Hz, 1H), 7.76 (, J = 1.34, 6.10 Hz, 1H), 7.93 (s, 1H).

(E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-(carboethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-one]benzoic acid (Compound D18)

To a solution of 3,4-dihydro-4,4-dimethyl-1-(carboethoxymethyl)-6-acetyl-naphthalene ((Compound D17, 25 mg, 0.10 mmol) and 4-carboxybenzaldehyde (17 mg, 0.13 mmol) in 2 ml of MeOH was added aqueous NaOH (0.75 ml, 12%). The reaction mixture was stirred at room temperature for overnight and quenched by addition of 10 % HCl to pH = 4.0. The solvent was removed and extracted ethyl acetate, the combined organic layer was washed with water. The organic layer was dried and concentrated to a white solid. This white solid was dissolved in 1 ml of DMF. To this solution was added DMAP (15.2 mg, 0.12 mmol), EDC (22 mg, 0.11 mmol) and

1 0.5 ml EtOH. The reaction mixture was stirred at room temperature  
2 for 5 h and concentrated in vacuo. The residue was passed through a  
3 chromatographic column with ethyl acetate/hexane (1/9) to give the  
4 title compound as a light tan solid.

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.21 (t,  $J = 7.14$  Hz, 3H), 1.36 (s, 6H), 1.42 (t,  $J$   
6  $= 7.14$  Hz, 3H), 2.33 (d,  $J = 4.46$  Hz, 2H), 4.13 (q,  $J = 7.14$  Hz, 2H),  
7 4.41 (q,  $J = 7.14$  Hz, 2H), 6.09 (t,  $J = 4.79$  Hz, 1H), 7.32 (d,  $J = 8.05$   
8 Hz, 1H), 7.60 (d,  $J = 15.6$  Hz, 1H), 7.70 (d,  $J = 8.36$  Hz, 2H), 7.80  
9 (s, 1H), 7.85 (d,  $J = 8.12$  Hz, 1H), 8.00 (d,  $J = 1.77$  Hz, 1H), 8.10 (d,  
10  $J = 8.36$  Hz, 2H).

11 3,4-Dihydro-4,4-dimethyl-6-acetyl-1-(1,1-dimethylethyl)naphthalene  
12 (Compound D19)

13 To a solution of 6-(2-methyl-1,3-dioxolan-2-yl)-3,4-dihydro-  
14 4,4-dimethylnaphthalen-1(2H)-one ((Compound D15, 353 mg, 1.36  
15 mmol) in 3 ml of dry ether at  $-78^\circ\text{C}$  was added dropwise t-BuLi (1  
16 ml, 1.7 mmol, 1.7 M solution in pentane). This clear light yellow  
17 solution was left at  $-78^\circ\text{C}$  for 30 min. Then, freshly distilled  $\text{SOCl}_2$   
18 (0.15 ml, 2.0 mmol) was added. The reaction mixture was stirred at  
19  $78^\circ\text{C}$  for additional 30 min and thereafter slowly warmed to room  
20 temperature. The reaction was quenched by addition of saturated  
21  $\text{NH}_4\text{Cl}$ . The white solids were removed by filtration and the clear  
22 solution was concentrated to an oil, and purified by column  
23 chromatography with ethyl acetate/hexane (1/10) to give the title  
24 compound as a yellow oil.

25  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.92 (d,  $J = 1.79$  Hz, 1H), 7.76 (dd,  $J = 1.80$ ,  
26 8.23 Hz, 1H), 7.73 (d,  $J = 8.23$  Hz, 1H), 6.10 (t,  $J = 4.98$  Hz, 1H),  
27 2.58 (s, 3H), 2.18 (d,  $J = 5.00$  Hz, 2H), 1.34 (s, 9H), 1.25 (s, 6H).

28  
29 (E)-4-[3-(3,4-Dihydro-4,4-dimethyl-1-(1,1-dimethyl-ethyl)naphth-6-  
30 yl)-prop-1-en-3-one]benzoic acid (Compound D20)

31 To a solution of 3,4-dihydro-4,4-dimethyl-6-acetyl-1-(1,1-



1 dimethylethyl)naphthalene (**Compound D19**, 60 mg, 0.234 mmol)  
2 and 4-carboxybenzaldehyde (35 mg, 0.233 mmol) in 5 ml of EtOH  
3 and 1 ml of THF was added 3 ml of 1 M aqueous NaOH. The  
4 yellow reaction mixture was left overnight when it turned red and  
5 then quenched with 6% HCl until it became yellow again. The  
6 solvent was removed and the residue was dissolved in ethyl acetate.  
7 The organic solution was washed with brine and dried. After  
8 evaporation of the solvent, the residue was purified by  
9 recrystallization from ethyl acetate to give 28 mg title compound as  
10 yellow crystals.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.15 (d, J = 8.31 Hz, 2H), 8.00 (d, J = 1.80 Hz,  
12 1H), 7.86 (dd, J = 1.83, 8.24 Hz, 1H), 7.83 (d, J = 15.82 Hz, 1H),  
13 7.78 (d, J = 8.48 Hz, 1H), 7.74 (d, J = 8.31 Hz, 2H), 7.65 (d, J =  
14 15.87 Hz, 1H), 6.13 (t, J = 5.0 Hz, 1H), 2.21 (d, J = 4.9 Hz, 2H),  
15 1.38 (s, 9H), 1.30 (s, 6H).

16 6-Bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
17 dimethylnaphthalene (Compound D21)

18 To a mixture of TiCl<sub>3</sub> (5 g, 32 mmol) of in 80 ml of dry DME  
19 under argon atmosphere was added in small portions lithium wire  
20 (0.80 g, 92 mmol). The reaction mixture was heated at 85 °C for 1 h  
21 and then cooled to room temperature. To the above solution was  
22 added a mixture of 6-bromo-3,4-dihydro-4,4-dimethylnaphthalen-  
23 1(2H)-one (**Compound H**, 1.00 g, 4.0 mmol) in 10 ml of dry DME  
24 and 10 ml of dry acetone through a cannula. The resulting mixture  
25 was heated to reflux and was left for 12 h and then cooled to room  
26 temperature. The reaction mixture was diluted with 80 ml of hexane  
27 and then filtered through florisil. Purification by column  
28 chromatography with pure hexane as the eluent gave the title  
29 compound as a clear oil.

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.23 (s, 6H), 1.60 t, J = 7.09 Hz, 2H), 1.82 (s,  
31 3H), 1.92 (s, 3H), 2.49 (t, J = 6.60 Hz, 2H), 7.10 (d, J = 8.30 Hz,

1H), 7.26 (dd, J = 1.95, 6.05 Hz, 1H), 7.40 (d, J = 2.08 Hz, 1H).

6-Acetyl-1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
3 dimethylnaphthalene (Compound D22)

4 To a solution of 6-bromo-1(2H)-(propyliden-2-yl)-3,4-dihydro-  
5 4,4-dimethylnaphthalene (Compound D21, 910 mg, 3.3 mmol) and  
6 bis(triphenylphosphine)palladium(II) chloride (100 mg, 0.14 mmol) of  
7 in 50 ml of DMF under argon was added (1-ethoxyvinyl)tributyl tin  
8 (1.713 ml, 5.07 mmol). The resulting reaction mixture was heated at  
9 85 °C for 48 h and cooled down to room temperature. The reaction  
10 was quenched with 15 ml of 10% HCl and then diluted with ethyl  
11 acetate. The organic layer was washed with brine and dried over  
12 MgSO<sub>4</sub>. Purification by column chromatography with pure hexane  
13 afforded the title compound as a yellow oil (410 mg).

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (s, 6H), 1.64 (t, J = 6.99 Hz, 2H), 1.86 (s,  
15 3H), 1.97 (s, 3H), 2.53 (t, J = 6.6 Hz, 2H), 2.61 (s, 3H), 7.31 (d, J =  
16 8.06 Hz, 1H), 7.74 (dd, J = 1.96, 6.10 Hz, 1H), 7.92 (d, J = 1.89 Hz,  
17 1H).

18  
19 (E)-4[3-{1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalen-  
20 6-yl}-prop-1-en-3-one]benzoic acid (Compound D23)

21 The title compound can be obtained by following the procedure  
22 employed for the preparation of (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-  
23 (carboethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-one]benzoic acid  
24 (Compound D18).

25 (+/-) 1-Hydroxy-6-(1,3-dioxolan-2-yl)-1,2,3,4-tetrahydro-4,4-  
26 dimethylnaphthalene (Compound D24)

27 To a solution of 6-(1,3-dioxolan-2-yl)-3,4-dihydro-4,4-  
28 dimethylnaphthalen-1(2H)-one (Compound D15, 110 mg, 0.42 mmol)  
29 in 6 ml of EtOH at 0 °C was added NaBH<sub>4</sub> (16 mg, 0.42 mmol). The  
30 reaction mixture was stirred for 4 h and kept in a freezer for  
31 overnight. The reaction was quenched with slow addition of cold

1 water and extracted with ethyl acetate. The organic layer was dried  
2 and concentrated to an oil. Purification by column chromatography  
3 with ethyl acetate/hexane (1/3) gave the title compound as a clear oil.  
4 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 3H), 1.34 (s, 3H), 1.65 (s, 3H), 1.61 (m,  
5 1H), 1.89 (m, 2H), 2.07 (m, 1H), 3.74 (m, 2H), 4.05 (m, 2H), 4.74 (t,  
6 J = 5.10 Hz, 1H), 7.30 (dd, J = 1.65, 6.16, 1H), 7.41 (d, J = 7.94 Hz,  
7 1H), 7.45 (d, J = 1.83 Hz, 1H).

8 (+/-) 1-Hydroxy-6-acetyl-1,2,3,4-tetrahydro-4,4-dimethyl-naphthalene  
9 **(Compound D25)**

10 A solution of 1-hydroxy-6-(1,3-dioxolan-2-yl)-1,2,3,4-  
11 tetrahydro-4,4-dimethylnaphthalene (**Compound D24**, 54.9 mg, 0.21  
12 mmol) in 3 ml of 10% HCl and 3 ml THF was heated at 100 °C for  
13 1.5 h and cooled to room temperature. The reaction mixture was  
14 diluted with ethyl acetate and neutralized with sat. NaHCO<sub>3</sub>. The  
15 organic layer was further washed with brine, dried and concentrated to  
16 an oil. Purification by column chromatography (silica) with ethyl  
17 acetate/hexane (1/9) gave the title compound as a clear oil (24.8 mg).  
18 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.34 (s, 3H), 1.66 (m, 1H), 1.89  
19 (m, 2H), 2.10 (m, 1H), 2.56 (s, 3H), 4.75 (t, J = 4.90, 1H), 7.54 (d, J  
20 = 8.18 Hz, 1H), 7.75 (dd, J = 1.83, 6.29 Hz, 1H), 7.94 (d, J = 1.77  
21 Hz, 1H).

22 (+/-) 1-(Methoxymethoxy)-6-acetyl-1,2,3,4-tetrahydro-4,4-dimethyl-  
23 naphthalene (Compound D26)

24 A solution of (+/-) 1-hydroxy-6-acetyl-1,2,3,4-tetrahydro-4,4-  
25 dimethyl-naphthalene (**Compound D25**, 24.8 mg, 0.11 mmol),  
26 chloromethyl methyl ether (0.12 mmol), triethyl amine (0.02 ml, 0.13  
27 mmol) and catalytic amount of tetrabutylammonium bromide in 2 ml  
28 of CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 5 h. Purification by  
29 column chromatography (silica) with ethyl acetate/hexane (1/10)  
30 afforded the title compound as an oil (17.8 mg).

31 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.95 (d, J = 1.7 Hz, 1H), 7.73 (dd, J = 1.7, 8.4

1 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.88 (d, J = 6.41 Hz, 1H), 4.76 (d,  
2 J = 6.41 Hz, 1H), 4.67 (m, 1H), 3.48 (s, 3H), 2.59 (s, 3H), 2.00 (m,  
3 3H), 1.58 (m, 1H), 1.37 (s, 3H), 1.29 (s, 3H).

4 (E)-4-[3-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-(methoxymethoxy)-  
5 naphthalen-6-yl)-prop-1-en-3-one]benzoic acid (Compound D27)

6 The title compound can be prepared by following the procedure  
7 employed for the preparation of (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-  
8 (carboethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-one]benzoic acid  
9 (Compound D18).

10 6-Acetyl-1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
11 dimethylnaphthalene (Compound D28)

12 To a solution of 6-(1,3-dioxolan-2-yl)]-3,4-dihydro-4,4-  
13 dimethylnaphthalen-1(2H)-one (Compound D15, 100 mg, 0.38  
14 mmol), NaOAc (78.8 mg, 0.95 mmol) in 5 ml of EtOH and 2 ml of  
15 THF was added methoxyamine hydrochloride (32.1 mg, 0.38 mmol).  
16 The resulting mixture was stirred at room temperature for overnight.  
17 The solvent was removed and the residue was dissolved in ethyl  
18 acetate (5 mL) and washed with saturated NaHCO<sub>3</sub>, water and brine.  
19 The solvent was distilled off and the crude product was purified by  
20 column chromatography with ethyl acetate/hexane (1/3) to give the  
21 title compound as an oil.

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.42 (s, 6H), 2.03 (t, J = 6.07 Hz, 2H), 2.24 (s,  
23 3H), 2.74 (t, J = 6.71 Hz, 2H), 4.04 (s, 3H), 7.56 (dd, J = 1.52, 6.72  
24 Hz, 1H), 7.70 (d, J = 1.75 Hz, 1H), 8.02 (d, J = 8.24 Hz, 1H).

25 (E)-4[3-{1(2H)-(O-methyl oxime)-3,4-dihydro-4,4-  
26 dimethylnaphthalen-6-yl}-prop-1-en-3-one]benzoic acid (Compound  
27 D29)

28 The title compound can be prepared by following the procedure  
29 employed for the preparation of (E)-4-[3-(3,4-dihydro-4,4-dimethyl-1-  
30 (carboethoxymethyl)-naphthalen-6-yl)-prop-1-en-3-one]benzoic acid  
31 (Compound D18).

1 3,4-dihydro-1-(trifluoromethylsulfonyl)oxy-4,4-dimethyl-6-(2-(2-  
2 methyl-1,3-dioxolanyl))naphthalene (Compound D30)

3 To a cold solution (-78° C) of 232.7 mg (1.267 mmol) of sodium  
4 bis(trimethylsilyl)amide in 2.0 ml of THF was added a solution of  
5 300.0 mg (1.154 mmol) of 6-(1,3-dioxolan-2-yl)-3,4-dihydro-4,4-  
6 dimethylnaphthalen-1(2H)-one (Compound D15) in 4.0 ml of THF.  
7 The reaction mixture was stirred at -78° C for 30 minutes and then a  
8 solution of 498.0 mg (1.269 mmol) of 5-chloro(2-bis-  
9 trifluoromethylsulfonyl)imide in 3.0 ml of THF was added. After  
10 stirring at -78° C for 1 hour, the solution was warmed to 0° C and  
11 stirred for 12 hours. The reaction was quenched by the addition of  
12 saturated aqueous NH<sub>4</sub>Cl. The mixture was extracted with EtOAc (50  
13 ml) and the combined organic layers were washed with saturated  
14 aqueous NaHCO<sub>3</sub>, water, and brine. The organic phase was dried  
15 over Na<sub>2</sub>SO<sub>4</sub> and then concentrated *in vacuo* to a yellow oil.  
16 Purification by column chromatography (silica, 10% EtOAc-hexanes)  
17 yielded the title compound as a clear yellow oil.

18 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.43 (1H, s), 7.38 (2H, m), 5.95 (1H, t, J =  
19 4.8 Hz), 4.07 (2H, m), 3.77 (2H, m), 2.42 (2H, d, J = 4.9 Hz), 1.66  
20 (3H, s), 1.32 (6H, s).

21 3,4-dihydro-1-(2-thienyl)-4,4-dimethyl-6-(2-(2-methyl-1,3-  
22 dioxolanyl))naphthalene (Compound D32)

23 A solution of 2-thienyllithium was prepared by the addition of  
24 106.9 mg (0.67 ml, 1.67 mmol) of n-butyl lithium (2.5 M solution in  
25 hexanes) to a cold solution (0° C) of 140.0 mg (1.67 mmol) of  
26 thiophene in 1.0 ml of THF. After stirring for 3 h a solution of  
27 364.0 mg (2.67 mmol) of zinc chloride in 2.0 ml of THF was added.  
28 The resulting solution was warmed to room temperature, stirred for 30  
29 minutes, and added via cannula to a solution of 262.0 mg (0.668  
30 mmol) of 3,4-dihydro-1-(trifluoromethylsulfonyl)oxy-4,4-dimethyl-6-  
31 (2-(2-methyl-1,3-dioxolanyl))naphthalene (Compound D30) and 30

1 mg (0.03 mmol) of tetrakis(triphenylphosphine)palladium(0) in 2.0 ml  
2 of THF. The resulting solution was heated at 50° C for 12 h, cooled  
3 to room temperature and diluted with saturated aqueous NH<sub>4</sub>Cl. The  
4 mixture was extracted with EtOAc and the combined organic layers  
5 were washed with water and brine. The organic phase was dried over  
6 Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to a yellow oil. Purification by  
7 column chromatography (10% EtOAc-hexanes) yielded the title  
8 compound as a yellow solid.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.48 (1H, d, J = 1.8 Hz), 7.34 (1H, d, J = 7.9  
10 Hz), 7.28 (2H, m), 7.08 (2H, m), 6.18 (1H, t, J = 4.8 Hz), 4.06 (2H,  
11 m), 3.82 (2H, m), 2.34 (2H, d, J = 4.8 Hz), 1.70 (3H, s), 1.34 (6H, s).

12 3,4-dihydro-1-(2-thienyl)-4,4-dimethyl-6-acetylnaphthalene  
13 (Compound D33)

14 A solution of 3,4-dihydro-1-(2-thienyl)-4,4-dimethyl-6-(2-(2-  
15 methyl-1,3-dioxolanyl))naphthalene (Compound D32, 103.0 mg, 0.32  
16 mmol) in 4.0 mL THF and 4.0 mL 10% aqueous HCl was refluxed  
17 for 1.5 h. Upon cooling to room temperature, the reaction mixture  
18 was diluted with EtOAc and washed with water and saturated aqueous  
19 NaCl. The organic layer was dried over MgSO<sub>4</sub> and the solvents were  
20 removed under reduced pressure to give the title compound as a  
21 colorless oil after column chromatography (10% EtOAc-hexanes).

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 7.98 (1H, d, J = 1.8 Hz), 7.75 (1H, dd, J =  
23 1.8, 8.1 Hz), 7.46 (1H, d, J = 8.1 Hz), 7.29 (1H, d, J = 5.0 Hz), 7.09  
24 (2H, m), 6.32 (1H, t, J = 4.8 Hz), 2.61 (3H, s), 2.38 (2H, d, J = 4.9  
25 Hz), 1.38 (6H, s).

26 4-[3-oxo-3-(7,8-dihydro-5-(2-thienyl)-8,8-dimethyl-2-naphthalenyl)-1-  
27 propenyl]-benzoic acid (Compound D34)

28 To a solution of 62.6 mg (0.222 mmol) 3,4-dihydro-1-(2-  
29 thienyl)-4,4-dimethyl-6-acetylnaphthalene (Compound D33) in 4.0  
30 mL of MeOH were added 33.4 mg (0.222 mmol) of 4-carboxy  
31 benzaldehyde, and 240.0 mg (6.00 mmol); 2.0 mL of 3M aqueous

1 NaOH). The resulting solution was stirred at room temperature for 12  
2 h, concentrated under reduced pressure, and the residual oil dissolved  
3 in EtOAc. The solution was treated with 10% HCl, and the organic  
4 layer washed with H<sub>2</sub>O, and saturated aqueous NaCl, before being  
5 dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced pressure  
6 gave the title compound as a pale green solid after recrystallization  
7 from EtOH.

8 <sup>1</sup>H NMR (acetone-d<sub>6</sub>) : δ 8.16 (1H, s), 8.10 (1H, d, J = 8.4 Hz),  
9 8.00 (5H, m), 7.84 (1H, d, J = 15.5 Hz), 7.48 (2H, m), 7.14 (2H, m),  
10 6.36 (1H, t, J = 4.8 Hz), 2.83 (1H, s), 2.43 (2H, d, J = 4.8 Hz), 1.39  
11 (6H, s).

12 Methyl-5,5-dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-  
13 carboxylate (Compound E2)

14 A degassed (with carbonmonoxide) solution of 2-bromo-5,5-  
15 dimethyl-5,6-dihydro-naphthalen-8(7H)-one (Compound G),  
16 palladium(II)-bis(triphenylphosphine)chloride (277 mg, 0.4 mmol),  
17 1,3-bis(diphenylphosphino)-propane (325 mg, 0.8 mmol), DMSO  
18 (30 mL), methanol (15 mL) and triethylamine (15 mL) was placed  
19 in an oil bath (70° C), under carbonmonoxide atmosphere) for  
20 16h. After dilution with water the mixture was extracted with ethyl  
21 acetate. The organic layer was washed with water, 10% HCl,  
22 saturated sodiumbicarbonate and brine. The organic layer was  
23 dried over MgSO<sub>4</sub>, and the solvent was removed by distillation.  
24 The residual crude material was purified by flash chromatography  
25 (silica, 1:4 ethyl acetate : hexane) to afford the title compound as  
26 a white solid.

27 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.42 (s, 6H), 2.05 (t, J = 6.6 Hz, 2H), 2.77  
28 (dd, J = 6.6, 2H), 3.93 (s, 3H), 7.52 (d, J = 8.3 Hz, 1H), 8.17 (dd,  
29 J = 1.8, 8.3 Hz, 1H), 8.67 (d, J = 1.8 Hz, 1H).

30 5,5-Dimethyl-5,6-dihydro-naphthalen-8(7H)-one-2-carboxylic acid  
31 (Compound E3)

1 To a solution of methyl-5,5-dimethyl-5,6-dihydro-  
2 naphthalen-8(7H)-one-2-carboxylate (**Compound E2**, 1.05 g, 4.5  
3 mmol) in 10 mL of ethanol and THF (10 mL) was added  
4 sodiumhydroxide 9 mL (1M solution). The solution was stirred for  
5 16 h and thereafter acidified with 10% HCl. The mixture was  
6 extracted with ethyl acetate, the combined organic layer was  
7 washed with water and brine, and dried over MgSO<sub>4</sub>. The solvent  
8 was distilled off under reduced pressure to afford the title  
9 compound as a white solid.

10 <sup>1</sup>HNMR (Acetone-D<sub>6</sub>) : δ 1.44 (s, 6H), 2.07 (t, J = 6.7 Hz, 2H),  
11 2.73 (t, J = 6.7 Hz, 2H), 7.70 (d, J = 8.2 Hz, 1H), 8.19 (dd, J =  
12 1.9, 8.2 Hz, 1H), 8.57 (d, J = 1.9 Hz, 1H).

13 Methyl 5,5-dimethyl-5,6-dihydro-8-(trifluoromethylsulfonyl)oxy-  
14 naphthalene -2-carboxylate (**Compound E4**)

15 To a solution of sodium bis(trimethylsilyl)amide (550.1 mg,  
16 3.00 mmol, 3.0 mL of a 1.0 M solution in THF) in 5.0 mL of THF  
17 at -78 °C was added 620.0 mg (2.67 mmol) of methyl-5,5-dimethyl-  
18 5,6-dihydro-naphthalen-8(7H)-one-2-carboxylate (**Compound E2**)  
19 in 8.0 mL of THF. After 30 min a solution of 1.15 g (2.94 mmol)  
20 of 2-*N,N*-bis(trifluoromethylsulfonyl)amino-5-chloropyridine in 6.0  
21 mL of THF was added. Stirring for 45 min at -78 °C was  
22 followed by warming to room temperature and stirring for 5 h.  
23 The reaction was quenched by the addition of saturated aqueous  
24 NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layers  
25 were washed with 5% aqueous NaOH and dried over MgSO<sub>4</sub>.  
26 Concentration of the dry solution under reduced pressure to an oil  
27 and column chromatography using 10% EtOAc-hexanes afforded  
28 the title compound as a yellow oil.

29 <sup>1</sup>H NMR(CDCl<sub>3</sub>) : δ 1.33 (s, 6H), 2.45 (d, J = 4.8 Hz, 2H), 3.93  
30 (s, 3H), 6.03 (t, J = 4.8 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 8.00  
31 (m, 2H).



1 Methyl 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalene-2-  
2 carboxylate (Compound E5)

3 To a solution of 329.0 mg (3.93 mmol) of thiophene in 2.0  
4 mL THF at 0 °C was added 251.8 mg (3.93 mmol, 1.56 mL of 2.5  
5 M solution in hexanes) of n-butyllithium. After stirring for 3 h at  
6 0 °C, a solution of 845.0 mg (6.28 mmol) of ZnCl<sub>2</sub> in 5.0 mL  
7 THF was added and the resulting solution stirred for 30 minutes.  
8 This solution was added to a second flask containing 570.0 mg  
9 (1.57 mmol) of methyl 5,5-dimethyl-5,6-dihydro-8-  
10 (trifluoromethylsulfonyl)oxy-naphthalene-2-carboxylate (Compound  
11 E4) and 76.0 mg (0.063 mmol) of  
12 tetrakis(triphenylphosphine)palladium(0) in 4.0 mL THF, and the  
13 resulting solution was heated to 50 °C for 3 h. Upon cooling to  
14 room temperature the reaction was quenched by the addition of  
15 saturated aqueous NH<sub>4</sub>Cl. Extraction with EtOAc was followed  
16 by washing of the combined organic layers with H<sub>2</sub>O and  
17 saturated aqueous NaCl, and drying over MgSO<sub>4</sub>. The dry  
18 solution was concentrated under reduced pressure and the title  
19 compound was isolated from the residue as a yellow oil by column  
20 chromatography (5-10% EtOAc / hexanes).  
21 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.34 (s, 6H), 2.35 (d, J = 4.9 Hz, 2H), 3.86  
22 (s, 3H), 6.23 (t, J = 4.9 Hz, 1H), 7.06 (m, 2H), 7.28 (m, 1H), 7.43  
23 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 1.7, 8.0 Hz, 1H), 8.06 (d, J =  
24 1.7 Hz, 1H).

25 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalene-2-carboxylic  
26 acid (Compound E6)

27 To a solution of methyl 5,5-dimethyl-5,6-dihydro-8-(2-  
28 thienyl)-2-naphthalenecarboxylate (Compound E5, 430.0 mg, 1.44  
29 mmol) in 3.0 mL of EtOH and 3.0 mL THF was added NaOH  
30 (240.0 mg, 6.00 mmol; 3.0 mL of a 2N aqueous solution). The  
31 resulting solution was warmed to 35 °C for 6 h, cooled to room

temperature and quenched with 1M HCl. The mixture was extracted with EtOAc and the combined organic layers washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure afforded the title compound as a pale yellow solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.34 (s, 6H), 2.38 (d, J = 4.8 Hz, 2H), 6.25 (t, J = 4.8 Hz, 1H), 7.12 (m, 3H), 7.45 (dd, J = 1.8, 4.7 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 1.8, 8.0 Hz, 1H), 8.06 (d, J = 1.8 Hz, 1H).

Ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-yl)carboxamido]-benzoate (Compound E7)

A solution of 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalene-2-carboxylic acid (Compound E6, 180.0 mg, 0.638 mmol), ethyl 4-aminobenzoate (137.0 mg, 0.829 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (160.0 mg, 0.829 mmol), and 4-N,N-dimethylaminopyridine (101.0 mg, 0.829 mmol) in 6.0 mL DMF was stirred overnight at room temperature. EtOAc (100 mL) was added and the solution washed with H<sub>2</sub>O, 5% HCl, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.

Removal of the solvents under reduced pressure and column chromatography (10-25% EtOAc-hexanes) of the residual oil afforded the title compound as a colorless solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.36 (s, 6H), 1.39 (t, J = 7.1 Hz, 3H), 2.38 (d, J = 4.8 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 6.27 (t, J = 4.8 Hz, 1H), 7.09 (m, 2H), 7.29 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.76 (dd, J = 1.9, 8.0 Hz, 1H), 7.83 (s, 1H), 7.88 (d, J = 1.9 Hz, 1H), 8.03 (d, J = 8.8 Hz, 2H).

4-[(5,5-Dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-yl)carboxamido]-benzoic acid (Compound E8)

To a solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(2-

1 thienyl)-naphthalen-2-yl)carboxamido]-benzoate (Compound E7,  
2 110.0 mg, 0.255 mmol) in 2.0 mL of EtOH and 1.0 mL THF was  
3 added NaOH (80.0 mg, 2.00 mmol; 2.0 mL of a 1N aqueous  
4 solution). After stirring overnight at room temperature the  
5 reaction was quenched by the addition of 1M aqueous HCl. The  
6 mixture was extracted with EtOAc and the combined organic  
7 layers washed with H<sub>2</sub>O and saturated aqueous NaCl before being  
8 dried over MgSO<sub>4</sub>. Removal of the solvents under pressure  
9 afforded the title compound as a pale yellow solid.

10 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.34 (s, 6H), 2.38 (d, J = 4.9 Hz, 2H),  
11 6.27 (t, J = 4.9 Hz, 1H), 7.12 (m, 2H), 7.44 (dd, J = 1.3, 5.0 Hz,  
12 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.88 (m, 3H), 8.02-7.91 (m, 3H),  
13 9.75 (s, 1H).

14 Ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
15 yl)carbonyl]oxy]-benzoate (Compound E9)

16 A solution of 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
17 naphthalene-2-carboxylic acid (Compound E6, 50.0 mg, 0.177  
18 mmol), ethyl 4-hydroxybenzoate (38.2 mg, 0.230 mmol), 1-(3-  
19 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44.0 mg,  
20 0.230 mmol), and 4-*N,N*-dimethylaminopyridine (28.0 mg, 0.230  
21 mmol) in 2.0 mL DMF was stirred overnight at room temperature.  
22 EtOAc (50 mL) was added and the solution washed with H<sub>2</sub>O,  
23 5% HCl, saturated aqueous NaCO<sub>3</sub>, and saturated aqueous NaCl  
24 before being dried over MgSO<sub>4</sub>. Removal of the sovents under  
25 reduced pressure and column chromatography (10% EtOAc-  
26 hexanes) of the residual oil afforded the title compound as a  
27 colorless solid.

28 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.36 (s, 6H), 1.39 (t, J = 7.2 Hz, 3H), 2.39  
29 (d, J = 4.9 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 6.26 (t, J = 4.9 Hz,  
30 1H), 7.09 (m, 2H), 7.25 (m, 2H), 7.49 (d, J = 8.2 Hz, 1H), 8.08  
31 (m, 3H), 8.22(d, J = 1.8 Hz, 1H).

1 2-trimethylsilylethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
2 naphthalen-2-yl)carbonyl]oxy]-benzoate (Compound E10)

3 A solution of 5,5-dimethyl-5,6-dihydro-8-(2-thienyl)-  
4 naphthalene-2-carboxylic acid (Compound E6, 79.0 mg, 0.280  
5 mmol), 2-trimethylsilylethyl 4-hydroxybenzoate (73.3 mg, 0.308  
6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
7 hydrochloride (70.0 mg, 0.364 mmol), and 4-*N,N*-  
8 dimethylaminopyridine (44.5 mg, 0.364 mmol) in 2.0 mL DMF was  
9 stirred overnight at room temperature. Et<sub>2</sub>O (100 mL) was added  
10 and the solution washed with H<sub>2</sub>O, 5% HCl, saturated aqueous  
11 NaCO<sub>3</sub>, and saturated aqueous NaCl before being dried over  
12 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and  
13 column chromatography (10% EtOAc-hexanes) of the residual oil  
14 afforded the title compound as a colorless solid.

15 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 0.10 (s, 9H), 1.15 (t, J = 8.2 Hz, 2H), 1.38 (s,  
16 6H), 2.39 (d, J = 4.0 Hz, 2H), 4.43 (t, J = 8.2 Hz, 2H), 6.28 (t, J  
17 = 4.0 Hz, 1H), 7.09 (m, 2H), 7.26 (m, 3H), 7.52 (d, J = 7.2 Hz,  
18 1H), 8.09 (m, 3H), 8.22 (s, 1H).

19 4-[(5,5-Dimethyl-5,6-dihydro-8-(2-thienyl)-naphthalen-2-  
20 yl)carbonyl]oxy]-benzoic acid (Compound E11)

21 To a solution of 2-trimethylsilylethyl 4-[(5,5-dimethyl-5,6-  
22 dihydro-8-(2-thienyl)-naphthalen-2-yl)carbonyl]oxy]-benzoate  
23 (Compound E10, 100.0 mg, 0.198 mmol) in 2.0 mL THF at room  
24 temperature was added 155.3 mg of tetrabutylammonium fluoride  
25 (0.594 mmol 0.6 mL of a 1M solution in THF). After stirring  
26 overnight the reaction was diluted with EtOAc and washed with  
27 H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
28 MgSO<sub>4</sub>. The solvents were removed under reduced pressure and  
29 the residue washed with hot acetonitrile leaving the product as a  
30 colorless solid.

31 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.37 (s, 6H), 2.42 (d, J = 4.8 Hz, 2H),

1 6.30 (t, J = 4.8 Hz, 1H), 7.14 (m, 2H), 7.37 (d, J = 8.6 Hz, 2H),  
2 7.44 (dd, J = 1.1, 5.0 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 8.12 (m,  
3 4H).

4 1(2H)-(Propyliden-2-yl)-3,4-dihydro-4,4-dimethylnaphthalene-7-  
5 carboxylic acid (Compound E12)

6 To a cold ( -78 °C) solution of 7-bromo-1(2H)-(propyliden-  
7 2-yl)-3,4-dihydro-4,4-dimethylnaphthalene (Compound A37, 640.0  
8 mg, 2.30 mmol) in 20 mL THF was added t-butyllithium (294.7  
9 mg, 4.60 mmol; 2.7 mL of a 1.7M solution in pentane). After 1 h  
10 dry CO<sub>2</sub> gas was bubbled through the solution for 1 h. The  
11 resulting mixture was allowed to warm to room temperature and  
12 then quenched with 10% aqueous HCl. The mixture was  
13 extracted with EtOAc and the combined organic layers washed  
14 with H<sub>2</sub>O and saturated aqueous NaCl before being dried over  
15 Na<sub>2</sub>SO<sub>4</sub>. Concentration of the dry solution under reduced  
16 pressure and washing of the residue with hexanes afforded the  
17 title compound as a pale yellow solid.

18 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.25 (s, 6H), 1.63 (t, J = 6.9 Hz, 2H),  
19 1.85 (s, 3H), 1.95 (s, 3H), 2.53 (t, J = 6.9 Hz, 2H), 7.43 (d, J =  
20 8.1 Hz, 1H), 7.82 (dd, J = 1.8, 8.1 Hz, 1H), 7.94 (d, J = 1.8 Hz,  
21 1H).

22 2-(Trimethylsilyl)ethyl-4-[(5,5-dimethyl-8(7H)-(propyliden-2-yl)-  
23 5,6-dihydronaphthalen-2-yl)]carbonyl}oxy]benzoate (Compound  
24 E13)

25 A solution of 5,5-dimethyl-5,6-dihydro-8(7H)-(1-propyliden-  
26 2-yl)-naphthalene-2-carboxylic acid (Compound E12, 70.0 mg,  
27 0.287 mmol), 2-trimethylsilylethyl 4-hydroxybenzoate (71.0 mg,  
28 0.298 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
29 hydrochloride (71.0 mg, 0.370 mmol), and 4-N,N-  
30 dimethylaminopyridine (45.0 mg, 0.370 mmol) in 2.0 mL DMF was  
31 stirred overnight at room temperature. Et<sub>2</sub>O (100 mL) was added

1 and the solution washed with H<sub>2</sub>O, 5% HCl, saturated aqueous  
2 NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried over  
3 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and  
4 column chromatography (5% EtOAc-hexanes) of the residual oil  
5 afforded the title compound as a colorless oil.  
6 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.14 (t, J = 8.4 Hz, 2H), 1.28 (s,  
7 6H), 1.66 (d, J = 6.9 Hz, 2H), 1.86 (s, 3H), 2.00 (s, 3H), 2.54 (t, J  
8 = 6.9 Hz, 2H), 4.30 (t, J = 8.4 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H),  
9 7.43 (d, J = 8.1 Hz, 1H), 7.97 (dd, J = 1.9, 8.1 Hz, 1H), 8.08 (d, J  
10 = 1.9 Hz, 1H), 8.11 (d, J = 8.7 Hz, 2H).  
11 4-[(5,5-Dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-2-  
12 yl)]carbonyloxybenzoic acid (Compound E14)

13 To a solution of 2-trimethylsilylethyl 4-[(5,5-dimethyl-5,6-  
14 dihydro-8(7H)-(propyliden-2-yl)-2-naphthalenyl)carbonyloxy]-  
15 benzoate (Compound E13, 84.0 mg, 0.181 mmol) in 2.0 mL THF at  
16 0 °C was added 130.7 mg of tetrabutylammonium fluoride (0.50  
17 mmol; 0.5 mL of a 1M solution in THF). After stirring at 0 °C for  
18 1.5 h and at room temperature for 4.5 h, the reaction was diluted  
19 with EtOAc and washed with H<sub>2</sub>O and saturated aqueous NaCl before  
20 being dried over MgSO<sub>4</sub>. The solvents were removed under reduced  
21 pressure and the residue crystalized from CH<sub>3</sub>CN to give the product  
22 as a colorless solid.

23 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.29 (s, 6H), 1.67 (t, J = 6.9 Hz, 2H), 1.87  
24 (s, 3H), 1.99 (s, 3H), 2.56 (t, J = 6.9 Hz, 2H), 7.43 (d, J = 8.6 Hz,  
25 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.97 (dd, J = 1.9, 8.2 Hz, 1H), 8.06 (d,  
26 J = 1.9 Hz, 1H), 8.14 (d, J = 8.7 Hz, 2H).

27 Ethyl 4-[(5,5-dimethyl-8(7H)-(propyliden-2-yl)-5,6-  
28 dihydronaphthalen-2-yl)]carbonyloxybenzoate (Compound E15)

29 A solution of 5,5-dimethyl-5,6-dihydro-8(7H)-(propyliden-2-  
30 yl)-2-naphthalenecarboxylic acid (Compound E12, 31.0 mg, 0.127  
31 mmol), ethyl 4-hydroxybenzoate (27.4 mg, 0.165 mmol), 1-(3-

1 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (31.6 mg,  
2 0.165 mmol), and 4-*N,N*-dimethylaminopyridine (20.2 mg, 0.165  
3 mmol) in 2.0 mL DMF was stirred overnight at room temperature.  
4 EtOAc (50 mL) was added and the solution washed with H<sub>2</sub>O, 5%  
5 HCl, saturated aqueous NaCO<sub>3</sub>, and saturated aqueous NaCl before  
6 being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced  
7 pressure and column chromatography (5% EtOAc-hexanes) of the  
8 residual oil afforded the title compound as a colorless oil.  
9 <sup>1</sup>H NMR(CDCl<sub>3</sub>) : δ 1.28 (s, 6H), 1.41 (t, J = 7.1 Hz, 2H), 1.66 (t, t  
10 J = 6.9 Hz, 2H), 1.86 (s, 3H), 2.00 (s, 3H), 2.56 (t, J = 6.9 Hz, 2H),  
11 4.40 (q, J = 7.1 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.1  
12 Hz, 1H), 7.98 (dd, J = 1.8, 8.1 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H),  
13 8.12 (d, J = 8.7 Hz, 2H).

14 Ethyl 4-[(5,5-dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-  
15 2-yl)]carboxamido]benzoate (Compound E16)

16 A solution of 1(2H)-(propyliden-2-yl)-3,4-dihydro-4,4-  
17 dimethylnaphthalene-7-carboxylic acid (Compound E12, 100.0 mg,  
18 0.410 mmol), ethyl 4-aminobenzoate (81.0 mg, 0.490 mmol), 1-(3-  
19 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (117.0 mg,  
20 0.615 mmol), and 4-*N,N*-dimethylaminopyridine (61.0 mg, 0.500  
21 mmol) in 3.0 mL DMF was stirred overnight at room temperature.  
22 EtOAc (100 mL) was added and the solution washed with H<sub>2</sub>O, 10%  
23 HCl, saturated aqueous NaCO<sub>3</sub>, and saturated aqueous NaCl before  
24 being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced  
25 pressure and column chromatography (10-15% EtOAc-hexanes) of the  
26 residual oil afforded the title compound as a colorless solid.  
27 <sup>1</sup>H NMR(CDCl<sub>3</sub>) : δ 1.29 (s, 6H), 1.40 (t, J = 7.1 Hz, 2H), 1.64 (t, J  
28 = 7.0 Hz, 2H), 1.86 (s, 3H), 2.00 (s, 3H), 2.52 (t, J = 6.6 Hz, 2H),  
29 4.37 (q, J = 7.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.63 (dd, J = 1.8,  
30 8.1 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 1.8 Hz, 1H), 7.92  
31 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H).

1 4-[(5,5-Dimethyl-8(7H)-(propyliden-2-yl)-5,6-dihydronaphthalen-2-  
2 yl)]carboxamido]benzoic acid (Compound E17)

3 To a solution of ethyl 4-[(5,5-dimethyl-8(7H)-(propyliden-2-  
4 yl)-5,6-dihydronaphthalen-2-yl)]carboxamido]benzoate (Compound  
5 E16, 25.0 mg, 0.064 mmol) in 3.0 mL of EtOH and 3.0 mL THF  
6 was added NaOH (80.0 mg, 2.00 mmol; 2.0 mL of a 1N aqueous  
7 solution). After stirring overnight at room temperature the reaction  
8 was quenched by the addition of 10% aqueous HCl. The mixture was  
9 extracted with EtOAc and the combined organic layers were washed  
10 with H<sub>2</sub>O and saturated aqueous NaCl and thereafter dried over  
11 Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under pressure and crystallization  
12 from CH<sub>3</sub>CN afforded the title compound as a colorless solid.

13 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.25 (s, 6H), 1.64 (t, J = 6.9 Hz, 2H), 1.85  
14 (s, 3H), 1.96 (s, 3H), 2.55 (t, J = 6.9 Hz, 2H), 7.45 (d, J = 8.1 Hz,  
15 1H), 7.78 (dd, J = 1.9, 8.1 Hz, 1H), 7.88 (d, J = 1.9 Hz, 1H), 7.95-  
16 8.05 (m, 4H), 9.71 (s, 1H).

17 Methyl-5,5-dimethyl-5,6-dihydro-8-(phenylthio)-naphthalene-2-  
18 carboxylate (Compound E18)

19 To a solution of methyl-5,5-dimethyl-5,6-dihydro-naphthalen-  
20 8(7H)-one-2-carboxylate (Compound E2, 835.0 mg, 3.60 mmol) in  
21 25.0 mL of THF at room temperature was added TiCl<sub>4</sub> (670.0 mg, 3.55  
22 mmol). Thereafter a solution of thiophenol (430.0 mg, 3.90 mmol) and  
23 Et<sub>3</sub>N (730.0 mg, 7.20 mmol) in 10 mL THF was added. The resulting  
24 brown mixture was stirred for 6 h before H<sub>2</sub>O was carefully added to  
25 quench the reaction. The product was extracted into Et<sub>2</sub>O and the  
26 combined organic layers washed with saturated aqueous NaCl and dried  
27 over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure afforded  
28 a solid from which the title compound was isolated as a yellow solid by  
29 column chromatography (5% EtOAc-hexanes).

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (s, 6H), 2.40 (d, J = 4.7 Hz, 2H), 3.85 (s,  
31 3H), 6.51 (t, J = 4.7 Hz, 1H), 7.10-7.36 (m, 5H), 7.38 (d, J = 8.1 Hz,



1 1H), 7.88 (dd, J = 1.8, 8.0 Hz, 1H), 8.30 (d, J = 1.8 Hz, 1H).

2 5,5-Dimethyl-5,6-dihydro-8-(phenylthio)-naphthalene-2-carboxylic  
3 acid (Compound E19).

4 To a solution of methyl 5,5-dimethyl-5,6-dihydro-8-  
5 (phenylthio)-naphthalene-2-carboxylate (Compound E18, 300.0 mg,  
6 0.926 mmol) in 4.0 mL of EtOH and 2.0 mL THF was added NaOH  
7 (200.0 mg, 5.00 mmol; 5.0 mL of a 1N aqueous solution). After  
8 stirring overnight at room temperature the reaction was quenched by  
9 the addition of 10% aqueous HCl. The mixture was extracted with  
10 EtOAc and the combined organic layers washed with H<sub>2</sub>O and  
11 saturated aqueous NaCl before being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of  
12 the solvents under pressure afforded the title compound as a yellow  
13 solid.

14 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.35 (s, 6H), 2.41 (d, J = 4.6 Hz, 2H), 6.54 (t, J  
15 = 4.6 Hz, 1H), 7.10-7.34 (m, 5H), 7.40 (d, J = 8.1 Hz, 1H), 7.92 (dd,  
16 J = 1.8, 8.1 Hz), 8.36 (d, J = 1.8 Hz, 1H).

17 Ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
18 yl)]carboxamidobenzoate (Compound E20)

19 A solution of 5,5-dimethyl-5,6-dihydro-8-(phenylthio)-  
20 naphthalene-2-carboxylic acid (Compound E19, 183.0 mg, 0.580  
21 mmol), ethyl 4-aminobenzoate (107.0 mg, 0.650 mmol), 1-(3-  
22 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144.0 mg,  
23 0.750 mmol), and 4-dimethylaminopyridine (85.0 mg, 0.700 mmol) in  
24 5.0 mL DMF was stirred overnight at room temperature. EtOAc (100  
25 mL) was added and the solution washed with H<sub>2</sub>O and saturated  
26 aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the  
27 solvents under reduced pressure and column chromatography (20%  
28 EtOAc-hexanes) of the residual oil afforded the title compound as a  
29 colorless solid.

30 <sup>1</sup>H NMR(CDCl<sub>3</sub>) : δ 1.37 (s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 2.45 (d, J  
31 = 4.7 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 6.65 (t, J = 4.7 Hz, 1H),

1 7.17-7.35 (m, 5H), 7.45 (d, J = 8.1 Hz, 1H), 7.52 (s, 1H), 7.60 (d, J =  
2 8.7 Hz, 2H), 7.77 (dd, J = 1.8, 8.1 Hz, 1H), 7.96 (d, J = 2.0 Hz, 1H),  
3 8.03 (d, J = 8.7 Hz, 2H).

4 4-[(5,5-Dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
5 yl)carboxamido]benzoic acid (Compound E21)

6 To a solution of ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-  
7 dihydronaphthalen-2-yl)}carboxamido]benzoate (Compound E20,  
8 90.0 mg, 0.196 mmol) in 3.0 mL of EtOH and 3.0 mL THF was  
9 added NaOH (120.0 mg, 3.00 mmol; 3.0 mL of a 1N aqueous  
10 solution). After stirring overnight at room temperature the reaction  
11 was quenched by the addition of 10% aqueous HCl. The mixture was  
12 extracted with EtOAc and the combined organic layers washed with  
13 H<sub>2</sub>O and saturated aqueous NaCl before being dried over Na<sub>2</sub>SO<sub>4</sub>.  
14 Removal of the solvents under pressure afforded the title compound as  
15 a pale yellow solid.

16 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.36 (s, 6H), 2.46 (d, J = 4.7 Hz, 2H), 6.11  
17 (t, J = 4.7 Hz, 1H), 7.13-7.36 (m, 5H), 7.51 (d, J = 8.0 Hz, 1H), 7.85  
18 (dd, J = 1.9, 8.0 Hz, 1H), 7.91-8.03 (m, 4H), 8.24 (d, J = 1.9 Hz,  
19 1H), 9.67 (s, 1H).

20 4-[(5,5-Dimethyl-8-(phenylsulfonyl)-5,6-dihydronaphthalen-2-  
21 yl)carboxamido]benzoic acid (Compound E22)

22 To a solution of 4-[(5,5-dimethyl-8-(phenylsulfonyl)-5,6-  
23 dihydronaphthalen-2-yl)carboxamido]benzoic acid (Compound E21,  
24 60.0 mg, 0.140 mmol) in 6.0 mL Et<sub>2</sub>O, 3.0 mL CH<sub>2</sub>Cl<sub>2</sub>, and 2.0 mL  
25 THF at 0 °C was added *m*-chloroperbenzoic acid (57-80%) (74-110  
26 mg, 0.430-0.640 mmol). The resulting solution was warmed to room  
27 temperature and stirred overnight. Water was added and the mixture  
28 extracted with EtOAc. The combined organic layers were washed with  
29 H<sub>2</sub>O and saturated aqueous NaCl before being dried over Na<sub>2</sub>SO<sub>4</sub>.  
30 Removal of the solvents under reduced pressure and crystallization of  
31 the residue from CH<sub>3</sub>CN afforded the title compound as a colorless

1 solid.

2  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.23 (s, 6H), 2.60 (d,  $J$  = 4.9 Hz, 2H), 7.51-  
3 7.62 (m, 5H), 7.89 (dd,  $J$  = 1.8, 7.9 Hz, 1H), 7.94 (s, 1H), 7.95-8.06  
4 (m, 6H), 8.61 (d,  $J$  = 1.9 Hz, 1H).

5 Ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
6 yl)]carbonyloxybenzoate (Compound E23)

7 A solution of 5,5-dimethyl-5,6-dihydro-8-(phenylthio)-  
8 naphthalene-2-carboxylic acid (Compound E19, 150.0 mg, 0.484  
9 mmol), ethyl 4-hydroxybenzoate (88.5 mg, 0.530 mmol), 1-(3-  
10 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (120.6 mg,  
11 0.630 mmol), and 4-*N,N*-dimethylaminopyridine (77.0 mg, 0.630  
12 mmol) in 5.0 mL DMF was stirred overnight at room temperature.  
13 EtOAc (50 mL) was added and the solution washed with  $\text{H}_2\text{O}$  and  
14 saturated aqueous NaCl before being dried over  $\text{MgSO}_4$ . Removal of  
15 the solvents under reduced pressure and column chromatography (10-  
16 15% EtOAc-hexanes) of the residual oil afforded the title compound  
17 as a colorless solid.

18  $^1\text{H}$  NMR( $\text{CDCl}_3$ ):  $\delta$  1.37(s, 6H), 1.40 (t,  $J$  = 7.1 Hz, 3H), 2.44 (d,  $J$  =  
19 4.8 Hz, 2H), 4.39 (q,  $J$  = 7.1 Hz, 2H), 6.57 (t,  $J$  = 4.8 Hz, 1H), 7.15-  
20 7.36 (m, 7H), 7.45 (d,  $J$  = 8.1 Hz, 1H), 8.01 (dd,  $J$  = 1.8, 8.1 Hz, 1H),  
21 8.10 (d,  $J$  = 8.7 Hz, 2H), 8.44 (d,  $J$  = 1.8 Hz, 1H).

22 Ethyl 4-[(5,5-dimethyl-8-(phenylsulfonyl)-5,6-dihydronaphthalen-2-  
23 yl)]carbonyloxybenzoate (Compound E24)

24 A solution of ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-  
25 dihydronaphthalen-2-yl)]carbonyloxybenzoate (Compound E23,  
26 50.0 mg, 0.109 mmol) in 5.0 mL  $\text{Et}_2\text{O}$  at 0  $^\circ\text{C}$  was added *m*-  
27 chloroperbenzoic acid (50%) (25 mg, 0.145 mmol). The resulting  
28 solution was warmed to room temperature and stirred overnight.  
29  $\text{Et}_2\text{O}$  was added and the organic layer washed with  $\text{H}_2\text{O}$ , saturated  
30 aqueous  $\text{NaHCO}_3$ , and saturated aqueous NaCl before being dried  
31 over  $\text{Na}_2\text{SO}_4$ . Removal of the solvents under reduced pressure and

1 and column chromatography (20% EtOAc-hexanes) afforded the title  
2 compound as a colorless solid.

3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.27 (s, 6H), 1.42 (t,  $J = 7.1$  Hz, 3H), 2.56 (d,  $J$   
4  $= 4.9$  Hz, 2H), 4.40 (q,  $J = 7.1$  Hz, 2H), 7.27 (d,  $J = 8.7$  Hz, 2H),  
5 7.43-7.57 (m, 5H), 8.02 (m, 3H), 8.14 (d,  $J = 8.7$  Hz, 2H), 8.68 (d,  $J$   
6  $= 1.7$  Hz, 1H).

7 2-(Trimethylsilyl)ethyl 4-[(5,5-dimethyl-8-(phenylthio)-5,6-  
8 dihydronaphthalen-2-yl)]carbonyl]oxy]benzoate (Compound E25)

9 A solution of 5,5-dimethyl-5,6-dihydro-8-(phenylthio)-  
10 naphthalene-2-carboxylic acid (Compound E19, 170.0 mg, 0.548  
11 mmol), 2-trimethylsilylethyl 4-hydroxybenzoate (130.0 mg, 0.548  
12 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
13 (126.0 mg, 0.657 mmol), and 4-*N,N*-dimethylaminopyridine (74.0 mg,  
14 0.600 mmol) in 4.0 mL DMF was stirred overnight at room  
15 temperature. EtOAc (100 mL) was added and the solution washed  
16 with  $\text{H}_2\text{O}$ , 10% HCl, and saturated aqueous NaCl before being dried  
17 over  $\text{MgSO}_4$ . Removal of the solvents under reduced pressure and  
18 column chromatography (5% EtOAc-hexanes) of the residual oil  
19 afforded the title compound as a colorless oil.

20  $^1\text{H}$  NMR( $\text{CDCl}_3$ ):  $\delta$  0.10 (s, 9H), 1.15 (t,  $J = 8.4$  Hz, 2H), 1.38 (s,  
21 6H), 2.44 (d,  $J = 4.7$  Hz, 2H), 4.43 (d,  $J = 8.4$  Hz, 2H), 6.58 (t,  $J =$   
22 4.7 Hz, 1H), 7.16-7.36 (m, 7H), 7.45 (d,  $J = 8.1$  Hz, 1H), 8.02 (dd,  $J$   
23  $= 1.8, 8.1$  Hz, 1H), 8.10 (d,  $J = 8.7$  Hz, 2H), 8.45 (d,  $J = 1.8$  Hz,  
24 1H).

25 4-[(5,5-Dimethyl-8-(phenylthio)-5,6-dihydronaphthalen-2-  
26 yl)]carbonyl]oxy]benzoic acid (Compound E26)

27 To a solution of 2-(trimethylsilyl)ethyl 4-[(5,5-dimethyl-5,6-  
28 dihydro-8-(phenylthio)-naphthalen-2-yl)carbonyl]oxy]-benzoate  
29 (Compound E25, 200.0 mg, 0.377 mmol) in 2.0 mL THF at 0 °C  
30 was added tetrabutylammonium fluoride (295.5 mg, 1.13 mmol; 1.13  
31 mL of a 1M solution in THF). After 2 h the solution was warmed

1 to room temperature and stirred overnight. EtOAc was added and the  
2 organic layer washed with H<sub>2</sub>O and saturated aqueous NaCl.  
3 Removal of the solvents under reduced pressure and recrystallization  
4 of the residue from CH<sub>3</sub>CN afforded the title compound as a pale  
5 yellow solid.

6 <sup>1</sup>H NMR(acetone-d<sub>6</sub>): δ 1.39 (s, 6H), 2.51 (d, J = 4.7 Hz, 2H), 6.67  
7 (t, J = 4.7 Hz, 1H), 7.19-7.38 (m, 6H), 7.61 (d, J = 8.1 Hz, 1H), 8.02  
8 (dd, J = 1.8, 8.1 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.43 (d, J = 8.1  
9 Hz, 1H).

10 4-[(5,5-Dimethyl-8-(phenylsulfonyl)-5,6-dihydronaphthalen-2-  
11 yl)]carbonyloxybenzoic acid (Compound E27)

12 To a solution of 4-[(5,5-dimethyl-5,6-dihydro-8-(phenylthio)-  
13 naphthalen-2-yl)carbonyloxy]-benzoic acid (Compound E26, 50.0  
14 mg, 0.116 mmol) in 3.0 mL CH<sub>2</sub>Cl<sub>2</sub>, and 1.0 mL THF at 0 °C was  
15 added *m*-chloroperbenzoic acid (57-80%) (34-52 mg, 0.197-0.299  
16 mmol). The resulting solution was warmed to room temperature and  
17 stirred overnight. Water was added and the mixture extracted with  
18 EtOAc. The combined organic layers were washed with H<sub>2</sub>O and  
19 saturated aqueous NaCl before being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of  
20 the solvents under reduced pressure and crystallization of the residue  
21 from CH<sub>3</sub>CN afforded the title compound as a colorless solid.

22 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.27 (s, 6H), 2.65 (d, J = 4.8 Hz, 2H), 7.14  
23 (d, J = 8.7 Hz, 2H), 7.57-7.68 (m, 5H), 8.03 (m, 3H), 8.17 (d, J = 8.7  
24 Hz, 2H), 8.77 (d, J = 1.8 Hz, 1H).

25 Ethyl 4-[(5,5-Dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-  
26 yl)]carboxamido]benzoate (Compound E28)

27 To a solution of 5,5-dimethyl-5,6-dihydro-8(7H)-one-  
28 naphthalene-2-carboxylic acid (Compound E3, 400.0 mg, 1.833  
29 mmol), ethyl 4-aminobenzoate (317.8 mg, 1.924 mmol), 1-(3-  
30 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (386.5 mg,  
31 2.016 mmol), and 4-dimethylaminopyridine (246.3 mg, 2.016 mmol)

1 in 18.0 mL CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 2h. EtOAc  
2 (25 mL) was added and the solution washed with H<sub>2</sub>O, 1M HCl, and  
3 saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of  
4 the solvents under reduced pressure and column chromatography (30%  
5 EtOAc-hexanes) of the residue afforded the title compound as a  
6 colorless solid.

7 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.41 (t, J = 7.1 Hz, 3H), 1.45 (s, 6H), 2.08 (t, J  
8 = 7.1 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H),  
9 7.62 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.6  
10 Hz, 2H), 8.14 (bs, 1H), 8.21 (dd, J = 2.1, 8.3 Hz, 1H), 8.42 (d, J =  
11 2.1 Hz, 1H).

12 4-[(5,5-Dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-yl)carboxamido]benzoic acid (Compound E29)  
13

14 A solution of ethyl 4-[(5,5-dimethyl-8(7H)-one-5,6-  
15 dihydronaphthalen-2-yl)carboxamido]benzoate (Compound E28; 50.0  
16 mg, 0.137 mmol) and NaOH (54.7 mg, 1.37 mmol; 0.68 mL of a 2N  
17 aqueous solution) in 2.0 mL EtOH and 1.0 mL THF was stirred at  
18 room temperature overnight. The reaction mixture was acidified with  
19 10% HCl and extracted with EtOAc. The combined organic layers  
20 were washed with H<sub>2</sub>O and saturated aqueous NaCl before being  
21 dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced pressure  
22 and crystallization of the residual solid from MeOH/H<sub>2</sub>O afforded the  
23 title compound as yellow crystals.

24 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.40 (s, 6H), 2.01 (t, J = 6.7 Hz, 2H), 2.74  
25 (t, J = 7.0 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.93 (m, 4H), 8.16 (dd,  
26 J = 2.1, 8.3 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 10.68 (s, 1H), 12.75  
27 (bs, 1H).

28 Ethyl 4-[(5,5-dimethyl-8(7H)-anti-(O-methyloxime)-5,6-  
29 dihydronaphthalen-2-yl)carboxamido]benzoate (Compound E30)

30 A mixture of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8(7H)-one-  
31 naphthalen-2-yl)carboxamido]-benzoate (Compound E28, 100.0 mg,

0.274 mmol), O-methylhydroxylamine hydrochloride (25.1 mg, 0.301 mmol), and NaOAc)3H<sub>2</sub>O (81.9 mg, 0.602 mmol) in 3.0 mL of EtOH was heated to 65 °C for 3 h and then stirred at room temperature for 68 h. The reaction was diluted with H<sub>2</sub>O and extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and column chromatography (20-30% EtOAc-hexanes) of the residue afforded the title compound as a colorless solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (s, 6H), 1.40 (t, J = 7.2 Hz, 2H), 1.75 (t, J = 7.0 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H), 4.04 (s, 3H), 4.37 (q, J = 7.1 Hz, 2H), 7.49 (d, J = 8.2 Hz, 1H), 7.76 (dd, J = 1.9, 8.7 Hz, 2H), 7.88 (dd, J = 2.1, 8.3 Hz, 1H), 8.06 (dd, J = 1.7, 8.7 Hz, 2H), 8.12 (bs, 1H), 8.40 (d, J = 2.0 Hz, 1H).

4-[(5,5-Dimethyl-8(7H)-anti-(O-methyloxime)-5,6-dihydronaphthalen-2-yl)carboxamido]benzoic acid (Compound E31)

A solution of ethyl (E)-4-[(5,5-dimethyl-5,6-dihydro-8(7H)-anti-(O-methyloxime)-naphthalen-2-yl)carboxamido]-benzoate (Compound E30, 31.4 mg, 0.080 mmol) and NaOH (31.8 mg, 0.796 mmol; 0.40 mL of a 2N aqueous solution) in 2 mL EtOH was stirred at room temperature overnight. The reaction was acidified with 10% HCL and extracted with EtOAc. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give an off-white solid. Crystallization from Et<sub>2</sub>O afforded the title compound as a colorless solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.27 (s, 6H), 1.69 (t, J = 6.9 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H), 3.96 (s, 3H), 7.58 (d, J = 8.3 Hz, 1H), 7.90 (m, 5H), 8.36 (d, J = 2.0 Hz, 1H), 10.57 (s, 1H), 12.73 (bs, 1H).

(+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoate (Compound E32)

A solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8(7H)-one-

naphthalen-2-yl)carboxamido]-benzoate (**Compound E28**, 125.0 mg, 0.342 mmol) in 2.0 mL EtOH and 2.0 mL THF was cooled to 0° C and treated with NaBH<sub>4</sub> (11.5 mg, 0.304 mmol). After 4 h the reaction was quenched by the careful addition of H<sub>2</sub>O, followed by 0.5 mL 1M HCl. EtOAc (25 mL) was added and the solution washed with 1M HCl, dilute aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O and saturated aqueous NaCl before being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced pressure afforded the title compound as a colorless solid.

<sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.28 (s, 3H), 1.31 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.65 (m, 1H), 1.88 (m, 3H), 4.32 (q, J = 7.1 Hz, 2H), 4.69 (q, J = 5.8 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.83 (dd, J = 2.2, 8.3 Hz, 1H), 7.99 (s, 4H), 8.09 (d, J = 1.9 Hz, 1H), 9.81 (bs, 1H).

(+/-) 4-[(5,5-Dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoic acid (**Compound E33**)

A mixture of (+/-) ethyl 4-[(5,5-dimethyl-5,6,7,8-tetrahydro-8-hydroxy-naphthalen-2-yl)carboxamido]-benzoate (**Compound E32**, 50.0 mg, 0.136 mmol) and NaOH (54.4 mg, 1.36 mmol; 0.68 mL of a 2N aqueous solution) in 3 mL EtOH was stirred at room temperature for 19h. The resulting solution was acidified with 10% HCl and extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl, and then dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced pressure afforded the title compound as a colorless solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.25 (s, 3H), 1.28 (s, 3H), 1.61 (m, 1H), 1.80 (m, 2H), 1.95 (m, 1H), 4.87 (m, 1H), 5.30 (bs, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.78 (dd, J = 1.9, 8.2 Hz, 1H), 7.49 (s, 4H), 8.01 (s, 1H), 10.47 (s, 1H), 12.72 (bs, 1H).

(+/-) Ethyl 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoate (**Compound E34**)

To a solution of (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-



1 tetrahydronaphthalen-2-yl)carboxamido]benzoate (**Compound E32**,  
2 57.0 mg, 0.155 mmol) in 5.0 mL  $\text{CH}_2\text{Cl}_2$  at 0 °C was added  
3 diisopropylethyl amine (276.2 mg, 2.137 mmol), chloromethyl methyl  
4 ether (37.7 mg, 0.469 mmol), and a catalytic amount of  
5 tetrabutylammonium iodide. The resulting solution was stirred at 45  
6 °C overnight. Upon cooling to room temperature the solution was  
7 diluted with EtOAc and washed with 5% HCl,  $\text{H}_2\text{O}$ , saturated  
8 aqueous  $\text{NaHCO}_3$ , and saturated aqueous NaCl, before being dried  
9 over  $\text{MgSO}_4$ . Removal of the solvents under reduced pressure,  
10 followed by column chromatography (15% EtOAc-hexanes) afforded  
11 the title compound as a colorless oil.

12  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.27 (s, 3H), 1.35 (s, 3H), 1.39 (t,  $J = 7.1$  Hz,  
13 3H), 1.64 (m, 1H), 1.90-2.13 (m, 3H), 3.48 (s, 3H), 4.36 (q,  $J = 7.1$   
14 Hz, 2H), 4.67 (t,  $J = 5.0$  Hz, 1H), 4.79 (d,  $J = 6.9$  Hz, 1H), 4.89 (d,  $J$   
15 = 6.9 Hz, 1H), 7.43 (d,  $J = 8.2$  Hz, 1H), 7.74 (m, 3H), 7.88 (d,  $J =$   
16 2.0 Hz, 1H), 8.03 (d,  $J = 8.7$  Hz, 2H), 8.18 (s, 1H).

17 (+/-) 4-[(5,5-Dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
18 tetrahydronaphthalen-2-yl)carboxamido]benzoic acid (**Compound**  
19 **E35)**

20 A mixture of (+/-) ethyl 4-[(5,5-dimethyl-8-(O-methoxymethyl)-  
21 5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoate (**Compound**  
22 **E34**, 30.0 mg, 0.073 mmol) and NaOH (40.0 mg, 1.00 mmol; 1.0 mL  
23 of a 1N aqueous solution) in 1.0 mL EtOH and 1.0 mL THF was  
24 stirred at room temperature overnight. The resulting solution was  
25 acidified with 10% HCl and extracted with EtOAc. The combined  
26 organic layers were washed with  $\text{H}_2\text{O}$  and saturated aqueous NaCl, and  
27 then dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvents under reduced  
28 pressure afforded the title compound as a colorless oil.

29  $^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.27 (s, 3H), 1.34 (s, 3H), 1.65 (m, 1H),  
30 1.95 (m, 2H), 2.08 (m, 1H), 3.42 (s, 3H), 4.66 (t,  $J = 5.0$  Hz, 1H),  
31 4.77 (d,  $J = 6.9$  Hz, 1h), 4.84 (d,  $J = 6.9$  Hz, 1h), 7.53 (d,  $J = 8.2$  Hz,

1H), 7.86 (dd, J = 2.0, 8.2 Hz, 1H), 8.00 (m, 5H), 9.78 (s, 1H).

2 2-(Trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-8(7H)-one-5,6-  
3 dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E36)

4 To a solution of 5,5-dimethyl-5,6-dihydro-8(7H)-one-  
5 naphthalene-2-carboxylic acid (Compound E3, 154.0 mg, 0.706  
6 mmol), 2-(trimethylsilyl)ethyl 4-hydroxybenzoate (185.0 mg, 0.777  
7 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
8 (176.0 mg, 0.918 mmol), and 4-dimethylaminopyridine (112.2 mg,  
9 0.918 mmol) in 4.0 mL DMF was stirred at room temperature  
10 overnight. EtOAc (100 mL) was added and the solution washed with  
11 H<sub>2</sub>O, 1M HCl, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous  
12 NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under  
13 reduced pressure and column chromatography (10% EtOAc-hexanes)  
14 of the residue afforded the title compound as a colorless solid.

15 <sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.15 (t, J = 8.3 Hz, 2H), 1.45 (s,  
16 6H), 2.08 (t, J = 7.0 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H), 4.43 (t, J =  
17 8.3 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.3 Hz, 1H), 8.12  
18 (d, J = 8.7 Hz, 2H), 8.30 (dd, 1H, J = 1.9, 8.3 Hz, 1H), 8.85 (d, J =  
19 1.9 Hz, 1H).

20 (+/-)-2-Trimethylsilylethyl 4-[[[(5,5-dimethyl-8-hydroxy-5,6,7,8-  
21 tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E37)

22 A solution of 2-(trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-8(7H)-  
23 one-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound  
24 E36, 160.0 mg, 0.365 mmol) in 2.0 mL EtOH and 2.0 mL THF was  
25 cooled to 0 °C and treated with NaBH<sub>4</sub> (13.8 mg, 0.365 mmol).

26 After 3 h the reaction was quenched by the careful addition of 5%  
27 aqueous HCl. EtOAc (100 mL) was added and the solution washed  
28 with H<sub>2</sub>O, dilute aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl  
29 before being dried over MgSO<sub>4</sub>. Removal of the solvents under  
30 reduced pressure followed by column chromatography (10-15%  
31 EtOAc) afforded the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.14 (t, J = 8.4 Hz, 2H), 1.30 (s, 3H), 1.37 (s, 3H), 1.68 (m, 1H), 1.92 (m, 2H), 2.12 (m, 1H), 4.45 (t, J = 8.4 Hz, 2H), 4.82 (m, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.3 Hz, 1H), 8.04 (dd, J = 2.0, 8.3 Hz, 1H), 8.11 (d, J = 8.7 Hz, 2H), 8.30 (d, J = 2.0 Hz, 1H).

(+/-) 2-(Trimethylsilyl)ethyl 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E38)

To a solution of (+/-) 2-trimethylsilylethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E37, 70.0 mg, 0.159 mmol) in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C were added diisopropylethylamine (276.2 mg, 2.137 mmol), and chloromethyl methyl ether (37.7 mg, 0.469 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with 5% HCl, H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl, before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure, followed by column chromatography (10% EtOAc-hexanes) afforded the title compound as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.14 (t, J = 8.3 Hz, 2H), 1.30 (s, 3H), 1.39 (s, 3H), 1.63 (m, 2H), 1.97 (m, 2H), 3.50 (s, 3H), 4.43 (t, J = 8.3 Hz, 2H), 4.71 (t, J = 5.0 Hz, 1H), 4.81 (d, J = 7.0 Hz, 1H), 4.91 (d, J = 7.0 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.3 Hz, 1H), 8.05 (dd, J = 1.8, 8.3 Hz, 1H), 8.10 (d, J = 8.7 Hz, 2H), 8.19 (d, J = 1.8 Hz, 1H).

(+/-) 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoic acid (Compound E39)

To a solution of (+/-) 2-trimethylsilylethyl-4-[(5,5-dimethyl-5,6,7,8-tetrahydro-8-(O-methoxymethyl)naphthalen-2-yl)carbonyl]oxy]-benzoate (Compound E38, 72.0 mg, 0.148 mmol) in

1 2.0 mL THF was added tetrabutylammonium fluoride (130.7 mg,  
2 0.500 mmol; 0.5 mL of a 1M solution in THF). The resulting  
3 solution was stirred overnight at room temperature, diluted with  
4 EtOAc, and washed with H<sub>2</sub>O and saturated aqueous NaCl. The  
5 solution was dried (MgSO<sub>4</sub>) and then concentrated under reduced  
6 pressure. The title compound was isolated as a colorless oil by  
7 preparative TLC (5% MeOH-CH<sub>2</sub>Cl<sub>2</sub>).  
8 <sup>1</sup>H MNR (acetone-d<sub>6</sub>): δ 1.30 (s, 3H), 1.37 (s, 3H), 1.67 (m, 1H),  
9 1.95 (m, 2H), 2.11 (m, 1H), 3.42 (s, 3H), 4.70 (t, J = 5.0 Hz, 1H),  
10 4.88 (d, J = 7.0 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.3  
11 Hz, 1H), 7.77 (d, J = 7.0 Hz, 2H), 8.03 (dd, J = 1.9, 8.3 Hz, 1H),  
12 8.15 (d, J = 8.7 Hz, 2H), 8.19 d, J = 1.9 Hz, 1H).

13 (+/-) Ethyl 4-[(5,5-dimethyl-8-hydroxy-5,6,7,8-tetrahydronaphthalen-  
14 2-yl)carbonyl]oxy]benzoic acid (Compound E40)

15 A solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8(7H)-one-  
16 naphthalen-2-yl)carbonyl]oxy]-benzoate (Compound E44, 126.0 mg,  
17 0.344 mmol) in 1.5 mL EtOH and 1.5 mL THF was cooled to 0 °C  
18 and treated with NaBH<sub>4</sub> (13.0 mg, 0.344 mmol). After 3 h the  
19 reaction was quenched by the careful addition of H<sub>2</sub>O. EtOAc (50  
20 mL) was added and the solution washed with H<sub>2</sub>O and saturated  
21 aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the  
22 solvents under reduced pressure followed by column chromatography  
23 (15-20% EtOAc) afforded the title compound as a colorless oil.

24 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.37 (s, 3H), 1.41 (t, J = 7.1 Hz,  
25 3H), 1.68 (m, 1H), 1.83-1.99 (m, 2H), 2.15 (m, 1H), 4.39 (q, J = 7.1  
26 Hz, 2H), 4.82 (m, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.3 Hz,  
27 1H), 8.05 (dd, J = 1.8, 8.3 Hz, 1H), 8.12 (d, J = 8.7 Hz, 2H), 8.29 (d,  
28 J = 1.8 Hz, 1H).

29 (+/-)Ethyl 4-[(5,5-dimethyl-8-(O-methoxymethyl)-5,6,7,8-  
30 tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E41)

31 To a solution of (+/-) ethyl 4-[(5,5-dimethyl-5,6,7,8-

1 tetrahydro-8-hydroxy-naphthalen-2-yl)carbonyl]oxy]-benzoate  
2 (**Compound E40**, 131.8 mg, 0.358 mmol) in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C  
3 was added diisopropylethylamine (277.5 mg, 2.147 mmol), and  
4 chloromethyl methyl ether (86.9 mg, 1.08 mmol). The resulting  
5 solution was stirred at room temperature overnight. The reaction  
6 mixture was diluted with EtOAc and washed with 10% HCl, H<sub>2</sub>O,  
7 saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl, before being  
8 dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure,  
9 followed by column chromatography (15% EtOAc-hexanes) afforded  
10 the title compound as a colorless oil.

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.38 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H),  
12 1.62 (m, 2H), 1.96 (m, 2H), 3.50 (s, 3H), 4.39 (q, J = 7.1 Hz, 2H), 4.71  
13 (t, J = 5.0 Hz, 1H), 4.80 d, J = 7.0 Hz, 1H), 4.92 (d, J = 7.0 Hz, 1H),  
14 7.28 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.3 Hz, 1H), 8.05 (dd, J = 1.8, 8.3  
15 Hz, 1H), 8.12 (d, J = 8.7 Hz, 2H), 8.19 (d, J = 1.8 Hz, 1H).

16 2-(Trimethylsilyl)ethyl-4-[[[(5,5-dimethyl-8(7H)-anti-(O-methyloxime)-  
17 5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (**Compound E42**)

18 A mixture of 2-(trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-5,6-  
19 dihydro-8(7H)-one-naphthalen-2-yl)carbonyl]oxy]-benzoate  
20 (**Compound E36**, 80.0 mg, 0.182 mmol), O-methylhydroxylamine  
21 hydrochloride (22.8 mg, 0.273 mmol), and NaOAc) X 3H<sub>2</sub>O (62.0  
22 mg, 0.455 mmol) in 3.0 mL of EtOH was stirred at room temperature  
23 for 5 days. The reaction was diluted with H<sub>2</sub>O and extracted with  
24 EtOAc. The combined organic layers were washed with H<sub>2</sub>O and  
25 saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of  
26 the solvents under reduced pressure and column chromatography (4-  
27 8% EtOAc-hexanes) of the residue, followed by preparative TLC  
28 (20% EtOAc-hexanes, afforded the title compound.

29 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.09 (s, 9H), 1.14 (t, J = 8.6 Hz, 2H), 1.33 (s,  
30 6H), 1.76 (t, J = 6.9 Hz, 2H), 2.82 (t, J = 6.9 Hz, 2H), 4.04 (s, 3H),  
31 4.43 (q, J = 8.4 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.3

1 Hz, 1H), 8.08 (dd, J = 1.9, 8.3 Hz, 1H), 8.12 (d, J = 8.7 Hz, 2H),  
2 8.78 (d, J = 1.9 Hz, 1H).

3 4-[[[(5,5-dimethyl-8(7H)-anti-(O-methyloxime)-5,6-dihydronaphthalen-  
4 2-yl)carbonyl]oxy]benzoic acid (Compound E43)

5 To a solution of (trimethylsilyl)ethyl 4-[[[(5,5-dimethyl-8(7H)-  
6 anti-(O-methyloxime)-5,6-dihydronaphthalen-2-  
7 yl)carbonyl]oxy]benzoate (**Compound E42**, 40.0 mg, 0.086 mmol) in  
8 1.5 mL THF was added tetrabutylammonium fluoride (68.0 mg, 0.260  
9 mmol; 0.26 mL of a 1M solution in THF). The resulting solution was  
10 stirred for 6 h at room temperature, diluted with EtOAc, and washed  
11 with H<sub>2</sub>O and saturated aqueous NaCl. The solution was dried  
12 (MgSO<sub>4</sub>) and then concentrated under reduced pressure. The title  
13 compound was isolated as a colorless oil by preparative TLC (5%  
14 MeOH-CH<sub>2</sub>Cl<sub>2</sub>).

15 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.34 (s, 6H), 1.78 (t, J = 7.0 Hz, 2H), 2.81  
16 (t, J = 7.0 Hz, 2H), 3.98 (s, 3H), 7.45 (d, J = 8.7 Hz, 2H), 7.67 (d, J  
17 = 8.3 Hz, 1H), 8.10 (dd, J = 1.9, 8.3 Hz, 1H), 8.15 (d, J = 8.7 Hz,  
18 2H), 8.74 (d, J = 1.9 Hz, 1H).

19 Ethyl 4-[[[(5,5-dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-  
20 yl)carbonyl]oxy]benzoate (Compound E44)

21 To a solution of 5,5-dimethyl-5,6-dihydro-8(7H)-one-2-  
22 naphthalenecarboxylic acid (**Compound E3**, 270.0 mg, 1.24 mmol),  
23 ethyl 4-hydroxybenzoate (226.0 mg, 1.364 mmol), 1-(3-  
24 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (309.0 mg,  
25 1.61 mmol), and 4-*N,N*-dimethylaminopyridine (197.0 mg, 1.61  
26 mmol) in 5.0 mL DMF was stirred at room temperature overnight.  
27 EtOAc (25 mL) was added and the solution washed with H<sub>2</sub>O, 1M  
28 HCl, and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>.  
29 Removal of the solvents under reduced pressure and column  
30 chromatography (7% EtOAc-hexanes) of the residue afforded the title  
31 compound as a pale-orange solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>): δ 1.41 (t, J = 7.1 Hz, 3H), 1.45 (s, 6H), 2.08 (t, J = 6.7 Hz, 2H), 2.80 (t, J = 6.7 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.7 Hz, 2H), 8.31 (dd, J = 1.8, 8.4 Hz, 1H), 8.04 (d, J = 1.8 Hz, 1H).

Ethyl 4-[[[(5,5-dimethyl-8(7H)-*anti*-(O-methyloxime)-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (**Compound E46**)

A mixture of ethyl 4-[[[(5,5-dimethyl-8(7H)-one-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate (**Compound E44**, 66.0 mg, 0.180 mmol), O-methylhydroxylamine hydrochloride (23.0 mg, 0.270 mmol), and NaOAc)3H<sub>2</sub>O (62.0 mg, 0.455 mmol) in 3.0 mL of EtOH was stirred at room temperature for 6 days. The reaction was diluted with H<sub>2</sub>O and extracted with EtOAc. The combined organic layers were washed with H<sub>2</sub>O and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and column chromatography (4-8% EtOAc-hexanes) of the residue, followed by preparative TLC (5% EtOAc-hexanes) afforded the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.33 (s, 6H), 1.41 (t, J = 7.1 Hz, 3H), 1.76 (t, J = 6.9 Hz, 2H), 2.82 (t, J = 6.9 Hz, 2H), 4.03 (s, 3H), 4.39 (q, J = 7.1 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.3 Hz, 1H), 8.11 (dd, J = 1.9, 8.3 Hz, 1H), 8.13 (d, J = 8.6 Hz, 2H), 8.78 (d, J = 1.9 Hz, 1H).

(+/-) Ethyl 2-(1-hydroxy-1,2,3,4-tetrahydro-4,4-dimethyl-7-bromonaphthalen-1-yl)acetate (**Compound E47**)

To a suspension of Zn (1.20 g, 18.4 mmol) in 10 mL benzene at 100 °C was slowly added a solution of ethyl 2-bromoacetate (658.0 mg, 3.94 mmol) and 3,4-dihydro-4,4-dimethyl-7-bromo-naphthalen-1(2H)-one (**Compound G**, 500.0 mg, 1.97 mmol) in 20.0 mL benzene. The resulting mixture was heated for 2 h, cooled to room temperature, and the solution decanted from the residual solids. The

solids were washed with EtOAc and the combined organic layers were washed with cold 15% H<sub>2</sub>SO<sub>4</sub>, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and column chromatography (10% EtOAc-hexanes) afforded the title compound as a yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 3H), 1.29 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.62-1.82 (m, 2H), 2.05 (m, 2H), 2.75 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.33 (dd, J = 2.1, 8.5 Hz, 1H), 7.71 (d, J = 2.1 Hz, 1H).

(+/-) Ethyl 2-(1-acetoxy-1,2,3,4-tetrahydro-4,4-dimethyl-7-bromo-naphthalen-1-yl)acetate (Compound E48)

To a solution of (+/-) ethyl 2-(1-hydroxy-1,2,3,4-tetrahydro-4,4-dimethyl-7-bromo-naphthalen-1-yl)acetate (Compound E47, 200.0 mg, 0.586 mmol) and 4-*N,N*-dimethylaminopyridine (86.0 mg, 0.703 mmol) in 4.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was added acetic anhydride (239.3 mg, 2.344 mmol). The resulting solution was warmed to room temperature and stirred overnight. The reaction was warmed to 50 °C for 3 h, cooled to room temperature, and diluted with EtOAc (70 mL). The solution was washed with H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, 10% aqueous HCl, and saturated aqueous NaCl, before being dried over MgSO<sub>4</sub>. Removal of the solvents under reduced pressure followed by column chromatography afforded the title compound as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.23 (t, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 1.76 (t, J = 6.9 Hz, 2H), 2.05 (s, 3H), 2.48 (m, 1H), 2.67 (m, 1H), 3.03 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 7.19 (d, J = 8.5 Hz, 1H), 7.33 (dd, J = 2.1, 8.5 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H).

(+/-) Ethyl 4-[(5,5-dimethyl-5,6,7,8-tetrahydro-8-acetoxy-8-carbethoxymethyl-naphthalen-2-yl)carboxamido]-benzoate (Compound E49)

A solution of ethyl 2-(1-acetoxy-1,2,3,4-tetrahydro-4,4-



1 dimethyl-7-bromo-naphthalen-1-yl)acetate (**Compound E48**, 450.0  
2 mg, 1.23 mmol), ethyl 4-aminobenzoate (810.0 mg, 4.90 mmol), 1,3-  
3 bis(diphenylphosphino)propane (100.0 mg, 0.245 mmol) in 5.0 mL  
4 Et<sub>3</sub>N, and 10.0 mL DMSO was sparged with CO (g) for 10 minutes.  
5 To this solution was added bis(triphenylphosphine)palladium(II)  
6 chloride (105.0 mg, 0.150 mmol). The solution was placed under 1  
7 atm of CO (balloon) and heated to 75 °C for 4 days. Upon cooling to  
8 room temperature the mixture was diluted with EtOAc and the  
9 solution washed with 10% HCl, H<sub>2</sub>O, and saturated aqueous NaCl  
10 before being dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under  
11 reduced pressure and column chromatography (5-25% EtOAc-  
12 hexanes) afforded the title compound.

13 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.20 (t, J = 7.1 Hz, 3H), 1.35 (s, 6H), 1.40 (t, J  
14 = 7.1 Hz, 3H), 1.78 (m, 2H), 2.03 (s, 3H), 2.50 (m, 1H), 2.71 (m,  
15 1H), 3.12 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H),  
16 7.42 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 1.9, 8.2 Hz, 1H), 7.73 (d, J =  
17 8.7 Hz, 2H), 7.95 (d, J = 1.9 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 8.20  
18 (s, 1H).

19 Ethyl (E)-4-[[[(5,5-dimethyl-5,6-dihydro-8(7H)-  
20 (carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate  
21 (**Compound E50a(trans)**);

22 Ethyl (Z)-4-[[[(5,5-dimethyl-5,6-dihydro-8(7H)-  
23 (carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate  
24 (**Compound E50a(cis)**) and

25 Ethyl (E)-4-[[[(5,5-dimethyl-5,6-dihydro-8-(carbethoxymethyl)-  
26 naphthalen-2-yl)carboxamido]-benzoate (**Compound E50b**)

27 To a solution of (+/-) ethyl 4-[(5,5-dimethyl-5,6,7,8-tetrahydro-  
28 8-acetoxy-8-carbethoxymethyl)-naphthalen-2-yl)carboxamido]-benzoate  
29 (**Compound E49**, 210.0 mg, 0.438 mmol) in 6.0 mL CH<sub>2</sub>Cl<sub>2</sub> was  
30 added 1,8-diazobicyclo[5.4.0]undec-7-ene (200.0 mg, 1.314 mmol).  
31 The resulting solution was stirred at room temperature for 21 h.

1 diluted with EtOAc, and the combined solution washed with 10%  
2 aqueous HCl and saturated aqueous NaCl before being dried over  
3 MgSO<sub>4</sub>. Removal of the solvents under reduced pressure and column  
4 chromatography (15% EtOAc-hexanes) afforded pure (Compound  
5 50b) and a mixture of Compound E50a(*trans*) and Compound  
6 E50a(*cis*). Compound E50a(*trans*) and Compound E50a(*cis*) were  
7 isolated using reverse phase HPLC (5% H<sub>2</sub>O-CH<sub>3</sub>CN), each as a  
8 colorless solid.

9 **Compound E50a(*trans*):**

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H), 1.40 (t, J  
11 = 7.1 Hz, 3H), 1.73 (t, J = 6.1 Hz, 2H), 3.21 (t, J = 6.1 Hz, 2H), 4.16  
12 (q, J = 7.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 6.35 (s, 1H), 7.46 (d, J  
13 = 8.1 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.82 (dd, J = 1.8, 8.1 Hz,  
14 1H), 8.04 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 1.8 Hz, 1H), 8.41 (s, 1H).

15 **Compound E50a(*cis*):**

16 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (t, J = 7.1 Hz, 3H), 1.34 (s, 6H), 1.40 (t, J  
17 = 7.1 Hz, 3H), 1.88 (t, J = 6.5 Hz, 2H), 2.61 (t, J = 6.5 Hz, 2H), 4.21  
18 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 5.92 (t, J = 1.1 Hz,  
19 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.88 (dd, J =  
20 1.9, 8.2 Hz, 1H), 8.06 (d, J = 8.7 Hz, 2H), 8.39 (s, 1H).

21 **(Compound 50b):**

22 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.19 (t, J = 7.1 Hz, 3H), 1.28 (s, 6H), 1.39 (t, J  
23 = 7.1 Hz, 3H), 2.26 (d, J = 4.5 Hz, 2H), 3.49 (s, 2H), 4.11 (q, J = 7.1  
24 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 5.97 (t, J = 4.5 Hz, 1H), 7.35 (d, J  
25 = 8.0 Hz, 1H), 7.70 (dd, J = 1.8, 8.0 Hz, 1H), 7.74 (m, 3H), 8.00 (d, J  
26 = 8.7 Hz, 2H), 8.41 (s, 1H).

27 (Z)-4-[(5,5-Dimethyl-5,6-dihydro-8(7H)-(carboxymethylidenyl)-  
28 naphthalen-2-yl)carboxamido]-benzoic acid (Compound E52)

29 A solution of ethyl (Z)-4-[(5,5-dimethyl-5,6-dihydro-8(7H)-  
30 (carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate  
31 (Compound E50a(*cis*), 15.0 mg, 0.034 mmol) and NaOH (80.0 mg,

1 2.00 mmol; 2.0 mL of a 1M aqueous solution) in 2.0 mL EtOH and  
2 1.0 mL THF was stirred overnight at room temperature. The reaction  
3 was quenched by the addition of 10% HCl and extracted with EtOAc.  
4 The combined organic layers were washed with H<sub>2</sub>O and saturated  
5 aqueous NaCl, and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents  
6 under reduced pressure and crystallization from CH<sub>3</sub>CN afforded the  
7 title compound as a colorless solid.

8 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.35 (s, 6H), 1.87 (t, j = 6.6 Hz, 2H), 2.61  
9 (m, 2H), 5.91 (t, J = 1.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.91-8.04  
10 (m, 5H), 8.29 (d, J = 1.9 Hz, 1H), 9.66 (s, 1H).

11 (E)-4-[[[(5,5-Dimethyl-5,6-dihydro-8(7H)-(carboxymethylidenyl)-  
12 naphthalen-2-yl)carboxamido]-benzoic acid (Compound E53)

13 A solution of ethyl (E)-4-[(5,5-dimethyl-5,6-dihydro-8(7H)-  
14 (carbethoxymethylidenyl)-naphthalen-2-yl)carboxamido]-benzoate  
15 (Compound E50a(*trans*), 20.0 mg, 0.046 mmol) and NaOH (160.0  
16 mg, 4.00 mmol; 4.0 mL of a 1M aqueous solution) in 3.0 mL EtOH  
17 and 1.0 mL THF was stirred overnight at room temperature. The  
18 reaction was quenched by the addition of 10% HCl and extracted with  
19 EtOAc. The combined organic layers were washed with H<sub>2</sub>O and  
20 saturated aqueous NaCl, and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the  
21 solvents under reduced pressure and crystallization from CH<sub>3</sub>CN  
22 afforded the title compound as a colorless solid.

23 <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.34 (s, 6H), 1.76 (t, J = 6.9 Hz, 2H), 3.24  
24 (m, 2H), 6.46 (t, J = 1.8 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.95-8.05  
25 (m, 5H), 8.29 (d, J = 1.9 Hz, 1H), 9.91 (s, 1H).

26 (+/-) Ethyl 4-[[[(5,5-dimethyl-8-hydroxy-8-(carbethoxy)-5,6,7,8-  
27 tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate (Compound E54)

28 To a suspension of Zn (500.0 mg, 7.65 mmol) in 10 mL  
29 benzene at 100 °C was slowly added a solution of ethyl 2-  
30 bromoacetate (150.3 mg, 0.900 mmol) and ethyl 4-[[[(5,5-dimethyl-  
31 8(7H)-one-5,6-dihydronaphthalen-2-yl)carbonyl]oxy]benzoate

1 (Compound E44, 110.0 mg, 0.300 mmol) in 10.0 mL benzene. The  
2 resulting mixture was heated for 2 h, cooled to room temperature, and  
3 the solution decanted from the residual solids. The solids were  
4 washed with EtOAc and the combined organic layers washed with  
5 cold 15% H<sub>2</sub>SO<sub>4</sub>, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous  
6 NaCl before being dried over MgSO<sub>4</sub>. Removal of the solvents under  
7 reduced pressure and column chromatography (15% EtOAc-hexanes)  
8 afforded the title compound as a pale-yellow oil.

9 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (t, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.37 (s,  
10 3H), 1.43 (t, J = 7.1 Hz, 3H), 1.72-1.90 (m, 2H), 2.11 (m, 2H), 2.84  
11 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 4.31 (s, 1H), 4.39 (q, J = 7.1 Hz,  
12 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.3 Hz, 1H), 8.03 (dd, J =  
13 1.8, 8.3 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.43 (d, J = 1.8 Hz, 1H).

14 Ethyl 4-[(5,5-dimethyl-8-(carbethoxy)-5,6-dihydronaphthalen-2-  
15 yl)carbonyl]oxy]benzoate (Compound E55)

16 To a solution of (+/-) ethyl 4-[(5,5-dimethyl-8-hydroxy-8-  
17 (carbethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]oxy]benzoate  
18 (Compound E54, 35.0 mg, 0.077 mmol) in 10 mL benzene was  
19 added a catalytic amount (approximately 2 mg) of *p*-toluenesulfonic  
20 acid monohydrate. The solution was heated to reflux under a Dean-  
21 Stark trap for 3 h, and then cooled to room temperature and stirred  
22 overnight. The solvent was removed under reduced pressure and the  
23 title compound isolated from the residue by column chromatography  
24 (10% EtOAc-hexanes).

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.21 (t, J = 7.1 Hz, 3H), 1.33 (s, 6H), 1.41 (t, J  
26 = 7.1 Hz, 3H), 2.31 (d, J = 4.6 Hz, 2H), 3.54 (s, 2H), 4.14 (q, J = 7.1  
27 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 6.01 (t, J = 4.6 Hz, 1H), 7.28 (d, J  
28 = 8.7 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 1.7 Hz, 1H), 8.04  
29 (dd, J = 1.7, 8.1 Hz, 1H), 8.13 (d, J = 8.7 Hz, 2H).

30 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
31 tetrahydropyranoxy)-5,5-

1 dimethyl-2-naphthoyloxy]benzoate (Compound E56a) and  
2 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-  
3 tetrahydropyranoxy)-5,5-  
4 dimethyl-2-naphthoyloxy]benzoate (Compound E56b)

5 To a solution of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-  
6 hydroxy-5,5-dimethyl-2-naphthoyloxy]benzoate (Compound E40, 243  
7 mg, 0.66 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) was added 3,4-  
8 dihydro-2H-pyran (184 mg, 2.2 mmol) followed by pyridinium p-  
9 toluenesulfonate (26 mg, 0.1 mmol). The reaction mixture was  
10 stirred at ambient temperature for 16 h, and diluted with  $\text{CH}_2\text{Cl}_2$   
11 (20 mL). The mixture was washed successively with water (5  
12 mL), saturated  $\text{NaHCO}_3$  (10 mL), water (10 mL) and brine (10  
13 mL). The organic phase was dried over  $\text{MgSO}_4$  and then  
14 concentrated *in vacuo* to a pale yellow oil. Purification by flash  
15 column chromatography (silica, 20% EtOAc-hexane) followed by  
16 HPLC separation (partisil 10, 10% EtOAc-hexane) afforded the  
17 title compounds as colorless oil.

18 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
19 tetrahydropyranoxy)-5,5-  
20 dimethyl-2-naphthoyloxy]benzoate (Compound E56a)  
21  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.28 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =  
22 7.1Hz, 3H), 1.51-2.11(m, 10H), 3.54-3.61 (m, 1H), 3.96-4.03 (m,  
23 1H), 4.35 (q, J = 7.1Hz, 2H), 4.70 (t, J = 5.0Hz, 1H), 4.87 (t, J =  
24 2.3Hz, 1H), 7.28 (d, J = 8.3Hz, 2H), 7.45 (d, J = 8.2Hz, 1H), 8.02  
25 (dd, J = 1.9, 8.3Hz, 1H), 8.10-8.13 (m, 3H).

26 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-  
27 tetrahydropyranoxy)-5,5-  
28 dimethyl-2-naphthoyloxy]benzoate (Compound E56b)

29  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.29 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =  
30 7.1Hz, 3H), 1.58-2.10(m, 10H), 3.57-3.63 (m, 1H), 4.01-4.08 (m,  
31 1H), 4.35 (q, J = 7.1Hz, 2H), 4.82 (t, J = 4.5Hz, 1H), 4.93 (t, J =

1 3.6Hz, 1H), 7.26 (d, J = 8.3Hz, 2H), 7.44 (d, J = 8.2Hz, 1H), 8.01  
2 (dd, J = 1.9, 8.3Hz, 1H), 8.10 (d, J = 8.6Hz, 2H), 8.37 (d, J =  
3 1.8Hz, 1H).

4 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)-  
5 tetrahydropyranoxy)-5,5-  
6 dimethyl-2-naphthoyloxy]benzoate (Compound E58a) and  
7 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)-  
8 tetrahydropyranoxy)-5,5-  
9 dimethyl-2-naphthoyloxy]benzoate (Compound E58b).

10 Employing the same general procedure as for the  
11 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-2(2'(R or S)-  
12 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate and  
13 ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-2(2'(S or R)-  
14 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate, ethyl 4-  
15 [5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethyl-2-  
16 naphthoyloxy]benzoate (Compound E40, 222 mg, 0.6mmol) was  
17 converted to a mixture of diastereomers using 3,4-dihydro-2H-  
18 pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26  
19 mg, 0.1 mmol). Purification by flash column chromatography  
20 (silica, 20% EtOAc-hexane) followed by HPLC separation  
21 (partisil 10, 10% EtOAc-hexane) afforded the title compounds as  
22 colorless oils.

23 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)-  
24 tetrahydropyranoxy)-5,5-  
25 dimethyl-2-naphthoyloxy]benzoate (Compound E58a):  
26 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =  
27 7.1Hz, 3H), 1.52-2.15(m, 10H), 3.54-3.61 (m, 1H), 3.96-4.03 (m,  
28 1H), 4.35 (q, J = 7.1Hz, 2H), 4.70 (t, J = 5.0Hz, 1H), 4.87 (t, J =  
29 2.3Hz, 1H), 7.26 (d, J = 8.3Hz, 2H), 7.46 (d, J = 8.3Hz, 1H), 8.02  
30 (dd, J = 1.9, 8.3Hz, 1H), 8.10-8.13 (m, 3H).

31 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)-

1 tetrahydropyranoxy)-5,5-  
2 dimethyl-2-naphthoyloxy]benzoate (Compound E58b)  
3 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.37 (t, J =  
4 7.1Hz, 3H), 1.57-2.10(m, 10H), 3.57-3.64 (m, 1H), 4.01-4.08 (m,  
5 1H), 4.35 (q, J = 7.1Hz, 2H), 4.82 (t, J = 4.5Hz, 1H), 4.94 (t, J =  
6 3.6Hz, 1H), 7.26 (d, J = 8.3Hz, 2H), 7.44 (d, J = 8.2Hz, 1H), 8.00  
7 (dd, J = 1.9, 8.3Hz, 1H), 8.10 (d, J = 8.6Hz, 2H), 8.36 (d, J =  
8 1.8Hz, 1H).

9 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
10 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
11 (Compound E60a) and  
12 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
13 R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
14 (Compound E60b)

15       Employing the same general procedure as for the  
16 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
17 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate and  
18 ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-  
19 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate, benzyl  
20 4-[5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethyl-2-  
21 naphthoyloxy]benzoate (Compound E82, 142 mg, 0.3mmol) was  
22 converted to a mixture of diastereomers using 3,4-dihydro-2H-  
23 pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26  
24 mg, 0.1 mmol). Purification by flash column chromatography  
25 (silica, 20% EtOAc-hexane) followed by HPLC separation  
26 (partisil 10 PAC, 10% EtOAc-hexane) afforded the title  
27 compounds as colorless oil.

28 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
29 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
30 (Compound 60a)

31 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.37 (s, 3H), 1.54-2.16 (m,

1 10H), 3.55-3.63 (m, 1H), 3.98-4.05 (m, 1H), 4.72 (t, J = 4.9Hz,  
2 1H), 4.89 (t, J = 4.6Hz, 1H), 5.39 (s, 2H), 7.28 (d, J = 8.6Hz,  
3 2H), 7.31-7.50 (m, 6H), 8.03 (dd, J = 1.9, 8.3Hz, 1H), 8.12-8.18  
4 (m, 3H).

5 Benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
6 R)tetrahydropyranoxy)-

7 5,5-dimethyl-2-naphthoyloxy]benzoate (**Compound E60b**)

8 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.35 (s, 3H), 1.54-2.08 (m,  
9 10H), 3.57-3.64 (m, 1H), 4.01-4.08 (m, 1H), 4.82 (t, J = 4.4Hz,  
10 1H), 4.94 (t, J = 3.9Hz, 1H), 5.37 (s, 2H), 7.27 (d, J = 6.8Hz,  
11 2H), 7.34-7.47 (m, 6H), 8.00 (dd, J = 2.0, 8.3Hz, 1H), 8.10 (d, J =  
12 9.2Hz, 2H), 8.36 (d, J = 1.9Hz, 1H).

13 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or

14 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate

15 (**Compound E62a**) and

16 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or

17 R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate

18 (**Compound E62b**)

19 Employing the same general procedure as for the  
20 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
21 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate and  
22 ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-  
23 tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate, benzyl  
24 4-[5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethyl-2-  
25 naphthoyloxy]benzoate (**Compound E82**, 142 mg, 0.3mmol) was  
26 converted to a mixture of diastereomers using 3,4-dihydro-2H-  
27 pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26  
28 mg, 0.1 mmol). Purification by flash column chromatography  
29 (silica, 20% EtOAc-hexane) followed by HPLC separation  
30 (partisil 10 PAC, 10% EtOAc-hexane) afforded the title  
31 compounds as colorless oils. Separation of the diastereomers gave



1 a 1:1 ratio of the title compounds both as colorless oils (RT = 32  
2 minutes and 39 minutes), respectively.

3 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
4 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
5 (Compound E62a):

6  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.37 (s, 3H), 1.52-2.15 (m,  
7 10H), 3.54-3.61 (m, 1H), 3.96-4.03 (m, 1H), 4.70 (t,  $J = 5.0\text{Hz}$ ,  
8 1H), 4.87 (t,  $J = 4.5\text{Hz}$ , 1H), 5.37 (s, 2H), 7.26 (d,  $J = 6.7\text{Hz}$ ,  
9 2H), 7.29-7.49 (m, 6H), 8.02 (dd,  $J = 1.9, 8.3\text{Hz}$ , 1H), 8.10-8.17  
10 (m, 3H).

11 Benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
12 R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
13 (Compound E62b):

14  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.35 (s, 3H), 1.54-2.10 (m,  
15 10H), 3.57-3.64 (m, 1H), 4.01-4.08 (m, 1H), 4.82 (t,  $J = 4.7\text{Hz}$ ,  
16 1H), 4.94 (t,  $J = 3.5\text{Hz}$ , 1H), 5.37 (s, 2H), 7.27 (d,  $J = 6.8\text{Hz}$ ,  
17 2H), 7.34-7.47 (m, 6H), 8.00 (dd,  $J = 2.0, 8.3\text{Hz}$ , 1H), 8.10 (d,  $J =$   
18  $9.2\text{Hz}$ , 2H), 8.36 (d,  $J = 1.9\text{Hz}$ , 1H).

19 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)-5,5-  
20 dimethyl-2-naphthoyloxy]benzoic acid (Compound E64)

21 To a solution of benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R  
22 or S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
23 (Compound E60a, 15 mg, 0.03 mmol) in ethyl acetate (5 mL) was  
24 added a catalytic amount of 10% Pd/C. The reaction mixture was  
25 then placed under a blanket of  $\text{H}_2$  by using a  $\text{H}_2$  balloon and  
26 stirred at ambient temperature for 12 h. The reaction mixture was  
27 then filtered through a plug of  $\text{MgSO}_4$  and the filtrate was  
28 concentrated under reduced pressure to give a white solid.  
29 Recrystallization from acetonitrile gave the title compound as a  
30 white solid.

31  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.30 (s, 3H), 1.37 (s, 3H), 1.51-2.17 (m,

1 10H), 3.57-3.64 (m, 1H), 3.98-4.06 (m, 1H), 4.72 (t, J = 4.9Hz,  
2 1H), 4.90 (t, J = 4.6Hz, 1H), 7.31 (dd, J = 2.5, 9.3Hz, 2H), 7.48  
3 (d, J = 8.3Hz, 1H), 8.04 (dd, J = 1.9, 8.3Hz, 1H), 8.13 (d, J =  
4 1.7Hz, 1H), 8.17 (dd, J = 2.4, 9.3Hz, 2H).

5 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)-5,5-  
6 dimethyl-2-naphthoyloxy]benzoic acid (Compound E65)

7 Employing the same general procedure as for the  
8 preparation of 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
9 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid  
10 (Compound E64), benzyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
11 R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
12 (Compound E60b, 15 mg, 0.03 mmol) was converted to the title  
13 compound (white solid).

14 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.36 (s, 3H), 1.55-2.11 (m,  
15 10H), 3.59-3.64 (m, 1H), 4.02-4.10 (m, 1H), 4.83 (t, J = 5.0Hz,  
16 1H), 4.95 (t, J = 3.7Hz, 1H), 7.29 (d, J = 8.7Hz, 2H), 7.4 (d, J  
17 = 8.3Hz, 1H), 8.01 (dd, J = 1.8, 8.2Hz, 1H), 8.16 (d, J = 8.6Hz,  
18 2H), 8.37 (d, J = 2.0Hz, 1H).

19 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)-5,5-  
20 dimethyl-2-naphthoyloxy]benzoic acid (Compound E66)

21 Employing the same general procedure as for the  
22 preparation of 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
23 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid  
24 (Compound E64), benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
25 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
26 (Compound E62a, 15 mg, 0.03 mmol) was converted to the title  
27 compound (white solid).

28 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (s, 3H), 1.36 (s, 3H), 1.53-2.15 (m,  
29 10H), 3.56-3.63 (m, 1H), 3.97-4.04 (m, 1H), 4.71 (t, J = 4.9Hz,  
30 1H), 4.89 (t, J = 4.3Hz, 1H), 7.30 (d, J = 8.8Hz, 2H), 7.47 (d, J  
31 = 8.4Hz, 1H), 8.03 (dd, J = 1.9, 8.2Hz, 1H), 8.11 (d, J = 2.0Hz,

1 1H), 8.17 (d, J = 8.6Hz, 2H).  
2 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)tetrahydropyranoxy)-5,5-  
3 dimethyl-2-naphthoyloxy]benzoic acid (Compound E67)

4 Employing the same general procedure as for the  
5 preparation of 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
6 S)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoic acid  
7 (Compound E64) benzyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
8 R)tetrahydropyranoxy)-5,5-dimethyl-2-naphthoyloxy]benzoate  
9 (Compound E62b, 15 mg, 0.03 mmol) was converted to the title  
10 compound (white solid).

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 3H), 1.37 (s, 3H), 1.55-2.09 (m,  
12 10H), 3.60-3.65 (m, 1H), 4.04-4.10 (m, 1H), 4.85 (t, J = 4.8Hz,  
13 1H), 4.96 (t, J = 3.8Hz, 1H), 7.31 (d, J = 8.6Hz, 2H), 7.46 (d, J =  
14 8.3Hz, 1H), 8.03 (dd, J = 1.9, 8.2Hz, 1H), 8.18 (d, J = 8.6Hz,  
15 2H), 8.38 (d, J = 1.7Hz, 1H).

16 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
17 S)tetrahydropyranoxy)5,5-  
18 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
19 E70a) and  
20 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
21 R)tetrahydropyranoxy)5,5-  
22 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
23 E70b)

24 Employing the same general procedure as for the  
25 preparation of ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)-  
26 tetrahydropyranoxy)-5,5-dimethyl-7-naphthoyloxy]benzoate and ethyl  
27 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-tetrahydropyranoxy)-  
28 5,5-dimethyl-7-naphthoyloxy]benzoate, (+/-) ethyl 4-[(5,5-dimethyl-  
29 8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)carboxamido]benzoate  
30 (Compound E32, 142 mg, 0.3mmol) was converted to a mixture of  
31 diastereomers using 3,4-dihydro-2H-pyran (184 mg, 2.2 mmol)

1 and pyridinium p-toluenesulfonate (26 mg, 0.1 mmol).

2 Purification by flash column chromatography (silica, 20% EtOAc-  
3 hexane) followed by HPLC separation (partisil 10 PAC, 20%  
4 EtOAc-hexane) of the diastereomers gave a 1:1 ratio of the title  
5 compounds, both as colorless oil (RT = 53 minutes and 60  
6 minutes), respectively.

7 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
8 S)tetrahydropyranoxy)5,5-  
9 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
10 **E70a**):

11 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (s, 3H), 1.30 (s, 3H), 1.34 (t, J =  
12 7.1Hz, 3H), 1.48-2.10 (m, 10H), 3.52-3.56 (m, 1H), 3.92-3.98 (m,  
13 1H), 4.30 (t, J = 7.1Hz, 2H), 4.61 (t, J = 4.8Hz, 1H), 4.80 (t, J =  
14 4.5Hz, 1H), 7.36 (d, J = 8.2Hz, 1H), 7.68-7.74 (m, 3H), 7.80 (d, J  
15 = 1.9Hz, 1H), 7.98 (d, J = 8.7Hz, 2H), 8.28 (s, 1H).

16 Ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or  
17 R)tetrahydropyranoxy)5,5-  
18 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
19 **E70b**):

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.26 (s, 3H), 1.32 (s, 3H), 1.36 (t, J =  
21 7.1Hz, 3H), 1.58-2.04 (m, 10H), 3.57-3.61 (m, 1H), 4.00-4.05 (m,  
22 1H), 4.31 (t, J = 7.1Hz, 2H), 4.78 (t, J = 4.9Hz, 1H), 4.86 (t, J =  
23 4.6Hz, 1H), 7.37 (d, J = 8.2Hz, 1H), 7.73-7.75 (m, 3H), 8.00-8.03  
24 (m, 3H), 8.34 (s, 1H).

25 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or  
26 S)tetrahydropyranoxy)5,5-  
27 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound  
28 **E72a**) and

29 Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or  
30 R)tetrahydropyranoxy)5,5-  
31 dimethylnaphthalene-2-yl)carboxamido]benzoate (Compound

**E72b)**

Employing the same general procedure as for the preparation of ethyl 4-[5,6,7,8-tetrahydro-8-(R or S)-(2'(R or S)-tetrahydropyranoxy)-5,5-dimethyl-7-naphthoyloxy]benzoate and ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)-tetrahydropyranoxy)-5,5-dimethyl-7-naphthoyloxy]benzoate, ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-hydroxy-5,5-dimethylnaphthalene-2-yl]carboxamido]benzoate (**Compound E32**, 142 mg, 0.3mmol) was converted to a mixture of diastereomers using 3,4-dihydro-2H-pyran (184 mg, 2.2 mmol) and pyridinium p-toluenesulfonate (26 mg, 0.1 mmol). Purification by flash column chromatography (silica, 20% EtOAc-hexane) followed by HPLC separation (partisil 10 PAC, 20% EtOAc-hexane) afforded the title compounds as colorless oil.

Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)5,5-dimethylnaphthalene-2-yl]carboxamido]benzoate (**Compound E72a**):

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.25 (s, 3H), 1.32 (s, 3H), 1.35 (t, J = 7.1Hz, 3H), 1.54-2.10 (m, 10H), 3.53-3.60 (m, 1H), 3.94-4.01 (m, 1H), 4.31 (t, J = 7.1Hz, 2H), 4.64 (t, J = 4.9Hz, 1H), 4.83 (t, J = 4.3Hz, 1H), 7.39 (d, J = 8.2Hz, 1H), 7.68-7.73 (m, 3H), 7.80 (d, J = 1.8Hz, 1H), 8.01 (d, J = 8.7Hz, 2H), 8.12 (s, 1H).

Ethyl 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)5,5-dimethylnaphthalene-2-yl]carboxamido]benzoate (**Compound E72b**)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.29 (s, 3H), 1.34 (s, 3H), 1.37 (t, J = 7.1Hz, 3H), 1.56-2.10 (m, 10H), 3.58-3.65 (m, 1H), 4.01-4.08 (m, 1H), 4.33 (t, J = 7.1Hz, 2H), 4.81 (t, J = 4.9Hz, 1H), 4.88 (t, J = 4.6Hz, 1H), 7.42 (d, J = 8.3Hz, 1H), 7.72-7.78 (m, 3H), 8.02-8.07

(m, 3H), 8.11 (s, 1H).

4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)tetrahydropyranoxy)5,5-dimethyl-naphthalene-2-yl]carboxamido]benzoic acid (Compound E74)

To a solution of ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)tetrahydropyranoxy)5,5-dimethylnaphthalene-2-yl]carboxamido]benzoate (Compound E70a, 54 mg, 0.12 mmol) in THF (2 mL) and methanol (1 mL) was added 0.5 M lithiumhydroxide (2 mL, 1 mmol). The reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was diluted with EtOAc (15 mL), and acidified with 10% HCl to pH 4. The organic layer was washed with water (5 mL), brine (10 mL), dried (MgSO<sub>4</sub>) and the solvent removed under reduced pressure. Recrystallization from EtOAc/hexane afforded the title compound as a white solid.

<sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.27 (s, 3H), 1.33 (s, 3H), 1.49-2.11 (m, 10H), 2.80 (br, 1H), 3.51-3.58 (m, 1H), 3.89-3.96 (m, 1H), 4.67 (t, J = 4.4Hz, 1H), 4.89 (t, J = 4.5Hz, 1H), 7.52 (d, J = 8.2Hz, 1H), 7.80 (d, J = 1.9Hz, 1H), 7.91-8.04 (m, 5H), 9.73 (s, 1H).

4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)tetrahydropyranoxy)5,5-dimethyl-naphthalene-2-yl]carboxamido]benzoic acid (Compound E75)

Employing the same general procedure as for the preparation of 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or S)tetrahydropyranoxy)5,5-dimethyl-naphthalene-2-yl]carboxamido]benzoic acid (Compound E74) ethyl 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(S or R)tetrahydropyranoxy)5,5-dimethyl-naphthalene-2-yl]carboxamido]benzoate (Compound E70b, 36 mg, 0.08 mmol) was converted into the title compound (white solid). <sup>1</sup>H NMR (acetone-d<sub>6</sub>): δ 1.28 (s, 3H), 1.34 (s, 3H), 1.51-2.02 (m, 10H), 2.80 (br, 1H), 3.55-3.60 (m, 1H), 3.96-4.03 (m, 1H), 4.77 (t,

1 J = 5.4Hz, 1H), 4.92 (t, J = 3.8Hz, 1H), 7.50 (d, J = 8.3Hz, 1H),  
2 7.82 (dd, J = 2.0, 8.3Hz, 1H), 7.97-8.02 (m, 4H), 8.09 (d, J =  
3 1.9Hz, 1H), 9.77 (s, 1H).

4 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(R or S)tetrahydropyranoxy)5,5-  
5 dimethyl-naphthalene-2-yl)carboxamido]benzoic acid (Compound  
6 E76)

7       Employing the same general procedure as for the  
8 preparation of 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
9 S)tetrahydropyranoxy)-5,5-dimethyl-naphthalene-2-  
10 yl)carboxamido]benzoic acid (Compound E74), ethyl 4-[5,6,7,8-  
11 tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)5,5- dimethyl-  
12 naphthalene-2-yl)carboxamido]benzoate (Compound E72b, 36 mg,  
13 0.08 mmol) was converted into the title compound (white solid).  
14 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (s, 3H), 1.34 (s, 3H), 1.55-2.08 (m,  
15 10H), 3.59-3.65 (m, 1H), 4.04-4.12 (m, 1H), 4.82 (t, J = 4.9Hz,  
16 1H), 4.88 (t, J = 2.6Hz, 1H), 7.43 (d, J = 8.3Hz, 1H), 7.74-7.81  
17 (m, 3H), 8.02 (d, J = 1.8Hz, 1H), 8.06 (d, J = 8.7Hz, 2H), 8.30 (s,  
18 1H).

19 4-[5,6,7,8-tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)5,5-  
20 dimethyl-naphthalene-2-yl)carboxamido]benzoic acid (Compound  
21 E77)

22       Employing the same general procedure as for the  
23 preparation of 4-[5,6,7,8-tetrahydro-8(S or R)-(2'(R or  
24 S)tetrahydropyranoxy)5,5-dimethyl-naphthalene-2-  
25 yl)carboxamido]benzoic acid (Compound E74), ethyl 4-[5,6,7,8-  
26 tetrahydro-8(R or S)-(2'(S or R)tetrahydropyranoxy)5,5- dimethyl-  
27 naphthalene-2-yl)carboxamido]benzoate (Compound E72a, 36 mg,  
28 0.08 mmol) was converted into the title compound (white solid).  
29 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.27 (s, 3H), 1.34 (s, 3H), 1.55-2.13 (m,  
30 10H), 3.57-3.63 (m, 1H), 3.97-4.03 (m, 1H), 4.70 (t, J = 4.7Hz,  
31 1H), 4.89 (t, J = 2.4Hz, 1H), 7.44 (d, J = 8.3Hz, 1H), 7.72-7.77

1 (m, 3H), 7.82 (d,  $J = 1.9\text{ Hz}$ , 1H), 8.06-8.10 M, 3H).

2 5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-2-  
3 naphthalenecarboxylic acid (Compound E78)

4 A solution of 7-bromo-1-(1,1-dimethylethyl)-3,4-dihydro-  
5 4,4-dimethylnaphthalene (Compound C42, 450.0 mg, 1.54 mmol)  
6 in 20 mL of THF was cooled to  $-78\text{ }^{\circ}\text{C}$  and 197.3 mg (3.08 mmol;  
7 1.8 mL of a 1.7M solution in pentane) added giving a pale-yellow  
8 solution. After 1h,  $\text{CO}_2$  (from evaporation of Dry Ice, dried with  
9  $\text{CaSO}_4$ ) was bubbled through the solution for 1h. After stirring at  
10  $-78\text{ }^{\circ}\text{C}$  for an additional hour, the reaction was quenched with  
11 10% aqueous HCl. The solution was extracted with EtOAc and  
12 the combined organic layers washed with  $\text{H}_2\text{O}$  and saturated  
13 aqueous NaCl before being dried over  $\text{Na}_2\text{SO}_4$ . Removal of the  
14 solvents under reduced pressure, and washing of the residue with  
15 hexanes afforded the title compound as a colorless solid.  
16  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.25 (6H, s), 1.38 (9H, s), 2.17 (2H, d,  $J =$   
17 4.9 Hz), 6.02 (1H, t,  $J = 4.9\text{ Hz}$ ), 7.41 (1H, d,  $J = 8.1\text{ Hz}$ ), 7.91  
18 (1H, dd,  $J = 1.6, 8.1\text{ Hz}$ ), 8.42 (1H, d,  $J = 1.6\text{ Hz}$ ).

19 Ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-2-  
20 naphthalenyl)carboxamido]-benzoate (Compound E79)

21 A solution of 5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-  
22 2-naphthalenecarboxylic acid (Compound E78, 150.0 mg, 0.581  
23 mmol), ethyl 4-aminobenzoate (115.2 mg, 0.697 mmol), 1-(3-  
24 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (145.0  
25 mg, 0.755 mmol), and 4-*N,N*-dimethylaminopyridine (89.0 mg,  
26 0.697 mmol) in 8.0 mL DMF was stirred overnight at room  
27 temperature. EtOAc (110 mL) was added and the solution  
28 washed with  $\text{H}_2\text{O}$ , 5% HCl, saturated aqueous  $\text{NaHCO}_3$ , and  
29 saturated aqueous NaCl before being dried over  $\text{MgSO}_4$ .  
30 Removal of the solvents under reduced pressure and column  
31 chromatography (10-25% EtOAc-hexanes) of the residual oil



1 afforded the title compound as a colorless solid.

2 <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.25 (6H, s), 1.39 (9H, s), 1.40 (3H, t, J = 7.1  
3 Hz), 2.18 (2H, d, J = 4.9 Hz), 4.37 (2H, q, J = 7.1 Hz), 6.05 (1H,  
4 t, J = 4.9 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.58 (1H, dd, J = 1.8, 8.0  
5 Hz), 7.24 (2H, d, J = 8.7 Hz), 7.91 (1H, s, ), 8.06 (2H, d, J = 8.7  
6 Hz), 8.26 (1H, d, J = 1.8 Hz).

7 4-[(5,5-dimethyl-5,6-dihydro-8-(1,1-dimethylethyl)-2-  
8 naphthalenyl)carboxamido]-benzoic acid (Compound E80)

9 To a solution of ethyl 4-[(5,5-dimethyl-5,6-dihydro-8-(1,1-  
10 dimethylethyl)-2-naphthalenyl)carboxamido]-benzoate (Compound  
11 E79, 50.0 mg, 0.123 mmol) in 2.0 mL of EtOH and 3.0 mL THF  
12 was added NaOH (240.0 mg, 6.00 mmol; 3.0 mL of a 2N aqueous  
13 solution). After stirring overnight at room temperature the  
14 reaction was quenched by the addition of 1M aqueous HCl. The  
15 mixture was extracted with EtOAc and the combined organic  
16 layers washed with H<sub>2</sub>O and saturated aqueous NaCl before being  
17 dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvents under reduced  
18 pressure afforded the title compound as a colorless solid.

19 <sup>1</sup>H NMR(d<sub>6</sub>-acetone) δ 1.24 (6H, s), 1.38 (9H, s), 2.17 (2H, d, J =  
20 4.9 Hz), 6.08 (1H, t, J = 4.9 Hz), 7.45 (1H, d, J = 8.1 Hz), 7.81  
21 (1H, dd, J = 1.8, 8.1 Hz), 7.97 - 8.05 (4H, m), 8.31 (1H, d, J = 1.8  
22 Hz).

23 Benzyl-4-[(5,5-dimethyl-5,6,7,8-tetrahydro-8-oxo-naphthalen-2-  
24 yl)carbonyl]oxy]-benzoate (Compound E81)

25 To a solution of 5,5-dimethyl-5,6,7,8-tetrahydro-8-oxo-  
26 naphthalen-2-carboxylic acid (Compound E3, 386 mg, 1.77 mmol)  
27 in dimethylformamide (4 mL) was added 1-(3-  
28 dimethylaminopropyl)-3-ethylcarboimide hydrochloride (440 mg,  
29 2.3 mmol) followed by dimethylamino pyridine (DMAP) (280 mg,  
30 2.3 mmol). The mixture was stirred for 10 minutes, and benzyl 4-  
31 hydroxy benzoate (426 mg, 1.9 mmol) was added and stirred at

1 ambient temperature for 16 hours. The mixture was diluted with  
2 ethyl acetate (100 mL) and washed with water (10 mL), brine (10  
3 mL), dried and solvent distilled off. The title compound was  
4 obtained as a pale yellow solid after chromatographic purification.  
5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.42 (s, 6H), 2.05 (t, J = 6.7 Hz, 2H), 2.77 (t,  
6 J = 6.7 Hz, 2H), 5.37 (s, 2H), 7.25-7.50 (m, 7H), 7.58 (d, J = 8.3  
7 Hz, 1H), 8.15 (d, J = 8.1 Hz, 2H), 8.28 (dd, J = 1.9, 8.3 Hz, 1H),  
8 8.82 (d, J = 1.9 Hz, 1H).

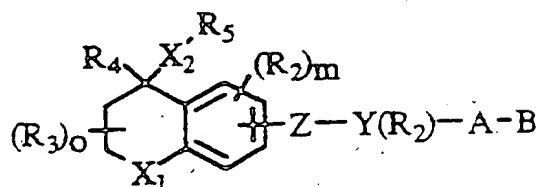
9 Benzyl-4-[[5,5-dimethyl-5,6,7,8-tetrahydro-8-hydroxy-naphthalen-2-  
10 yl)carbonyl]oxy]-benzoate (Compound E82)

11 To a solution of benzyl-4-[[5,5-dimethyl-5,6,7,8-tetrahydro-8-  
12 oxo-naphthalen-2-yl)carbonyl]oxyl]-benzoate ((Compound E81, 377  
13 mg, 0.88 mmol) in dimethoxyethane (20 mL) was added  
14 sodiumborohydride (33 mg, 0.9 mmol). The mixture was stirred  
15 for 12 hours at room temperature. The mixture was diluted with  
16 ethylacetate (50 mL), washed with water (10 mL), brine (10 mL),  
17 dried and solvent distilled off. The title compound was obtained  
18 as a white solid after chromatographic purification.

19 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H), 1.37 (s, 3H), 1.60-1.75 (m, 1H),  
20 1.85-2.00 (m, 2H), 2.05-2.20 (m, 1H), 2.30 (brs, 1H), 4.81 (t, J =  
21 5.6, 1H), 5.38 (s, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.35-7.51 (m, 6H),  
22 8.04 (dd, J = 1.9, 8.3 Hz, 1H), 8.15 (d, J = 8.7 Hz, 2H), 8.31 (d, J  
23 = 1.9 Hz).

## WHAT IS CLAIMED IS:

1. A compound of the formula



wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to 6 carbons, and  $n$  is an integer between 0 and 2;

$X_2$  is S or O;

$Z$  is  $-N=N-$ ,

$-N(O)=N-$ ,

$-N=N(O)-$ ,

$-N=CR_1-$ ,

$-CR_1=N$ ,

$-(CR_1=CR_1)_n-$  where  $n'$  is an integer having the value 0 - 5,

$-CO-NR_1-$ ,

$-CS-NR_1-$ ,

$-NR_1-CO$ ,

$-NR_1-CS$ ,

$-COO-$ ,

$-OCO-$ ;

$-CSO-$ ;

$-OCS-$ ;

$-CO-CR_1=CR_1-$ ;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $CF_3$ , fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons;

- 1  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;  
 2  $m$  is an integer having the value of 0 - 3;  
 3  $o$  is an integer having the value of 0 - 4;  
 4  $R_4$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons  
 5 and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to  
 6 3 triple bonds, carbocyclic aryl selected from the group consisting of  
 7 phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 -$   
 8  $C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl; CN,  $(CH_2)_pCO_2H$  or  $(CH_2)_pCO_2R_8$  where  
 9  $p$  is an integer between 0 to 10;  
 10  $R_5$  is hydrogen, alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1  
 11 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double  
 12 bonds, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbo-  
 13 cyclic aryl selected from the group consisting of phenyl,  $C_1 -$   
 14  $C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 - C_{10}$ alkyl,  
 15 naphthyl- $C_1 - C_{10}$ alkyl;  $Si(C_{1-6}alkyl)_3$ ,  $COR_{14}$ , camphanoyl,  
 16  $C(R_{15})(R_{16})X_2R_{17}$ ;  
 17  $Y$  is a phenyl or naphthyl group, or heteroaryl selected from a group  
 18 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 19 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 20 groups being optionally substituted with one or two  $R_2$  groups, or  
 21 when  $Z$  is  $-(CR_1=CR_1)_n-$  and  $n'$  is 3, 4 or 5 then  $Y$  represents a  
 22 direct valence bond between said  $(CR_2=CR_2)_n$  group and B;  
 23  $A$  is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having  
 24 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons  
 25 and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple  
 26 bonds;  
 27  $B$  is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
 28  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  
 29  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
 30 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 31 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl

1 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
2 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
3 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
4 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
5 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
6 divalent alkyl radical of 2-5 carbons;

7  $R_{14}$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons  
8 and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to  
9 3 triple bonds, carbocyclic aryl selected from the group consisting of  
10 phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 -$   
11  $C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl, and

12  $R_{15}$  and  $R_{16}$  are hydrogen or lower alkyl of 1 to 6 carbons,  $R_{17}$  is  
13 lower alkyl of 1 to 6 carbons, or  $R_{16}$  and  $R_{17}$  jointly form a ring having a  
14 total of 4 to 5 carbons and the  $X_2$  heteroatom.

15 2. A compound in accordance with Claim 1 wherein Y is selected  
16 from the group consisting of phenyl, naphthyl, pyridyl, thienyl and furyl.

17 3. A compound in accordance with Claim 2 wherein Y is phenyl.

18 4. A compound in accordance with Claim 2 wherein Y is  
19 naphthyl.

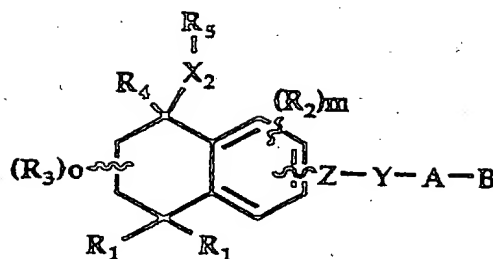
20 5. A compound in accordance with Claim 1 where n is 1.

21 6. A compound in accordance with Claim 1 where Z is selected  
22 from the groups consisting of  $-(CR_1=CR_1)_{n'}$ ,  $-N=N-$ ,  $-CO-CR_1=CR_1-$ ,  $-$   
23  $COO-$ , and  $-CONH-$  where  $n'$  is 0, 1, or 3 with the proviso that when  
24  $n'$  is 3 then Y represents a direct valence bond between the  
25  $-(CR_1=CR_1)_{n'}$  group and the -A-B group.

26 7. A compound in accordance with Claim 1 where A is  $(CH_2)_q$ .

27 8. A compound in accordance with Claim 1 where B is COOH or  
28 a pharmaceutically acceptable salt thereof,  $COOR_9$ , or  $CONR_9R_{10}$ .

29 9. A compound of the formula  
30  
31



where  $R_1$  is independently H or alkyl of 1 to 6 carbons;

$X_2$  is S or O;

Z is  $-N=N-$ ,

$-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 3,

$-CO-NH-$ ,

$-COO-$ ,

$-CO-CR_1=CR_1-$ ;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons;

$R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

$m$  is an integer having the value of 0 - 3;

$o$  is an integer having the value of 0 - 4;

Y is phenyl, naphthyl, pyridyl or thienyl with the proviso that when  $n'$  is 3 then Y represents a direct valence bond between the Z and A-B groups;

A is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,

where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$

independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is divalent alkyl radical of 2-5 carbons;

$R_4$  is hydrogen, alkyl of 1 to 10 carbons,  $CH_2COOH$  or  $CH_2CO_2R_8$ ;

$R_5$  is hydrogen, alkyl of 1 to 10 carbons, 2-tetrahydropyranyl,  $CH_2OCH_3$  or  $COR_{12}$ .

10. A compound in accordance with Claim 9 where Y is phenyl.

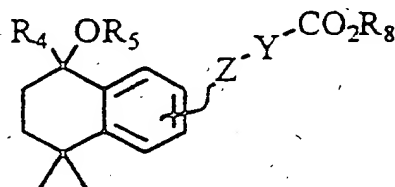
11. A compound in accordance with Claim 9 where Y is naphthyl.

12. A compound in accordance with Claim 9 where A is  $(CH_2)_q$  where q is 0 and where B is  $COOH$  or a pharmaceutically acceptable salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

13. A compound in accordance with Claim 9 where  $R_4$  is H  $CH_2COOH$  or  $CH_2COOR_8$ .

14. A compound in accordance with Claim 9 where  $R_5$  is H, 2-tetrahydropyranyl or  $CH_2OCH_3$ .

15. A compound of the formula



where Z is  $-CH=CH-$ ,  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$ ,  $-N=N-$ ,  $CO-CH=CH-$ ,  $CONH-$ , or  $COO-$ ;

Y is phenyl or when Z is  $(CH_3)=CH-CH=CH-C(CH_3)=CH-$  then Y represents a direct valence bond between Z and  $CO_2R_8$ ,

$R_4$  is H,  $CH_2COOH$ ,  $CH_2COOR_8$ , or lower alkyl of 1 - 6 carbons,

$R_5$  is H,  $CH_2OCH_3$ ,  $COCH_3$  or 2-tetrahydropyranyl, and

$R_8$  is hydrogen or lower alkyl.

1 16. A compound in accordance with Claim 15 where the Z group  
2 is connected to the 2-position of the tetrahydronaphthalene ring.

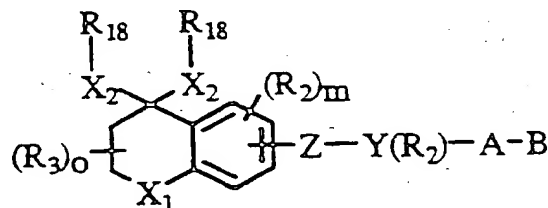
3 17. A compound in accordance with Claim 15 where the Z group  
4 is connected to the 3-position of the tetrahydronaphthalene ring.

5 18. A compound in accordance with Claim 17 where Z is CO-  
6 CH=CH.

7 19. A compound in accordance with Claim 16 where Z is -  
8 CH=CH, C(CH<sub>3</sub>)=CH-CH=CH-C(CH<sub>3</sub>)=CH-, -N=N-, CONH, or  
9 COO.

10 20. A compound in accordance with Claim 15 where R<sub>8</sub> is H or  
11 ethyl.

12 21. A compound of the formula



21 wherein X<sub>1</sub> is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> where R<sub>1</sub> is independently H or alkyl of 1 to  
22 6 carbons, and n is an integer between 0 and 2;

23 X<sub>2</sub> is S or O;

24 Z is -N=N-,

25 -N(O)=N-,

26 -N=N(O)-,

27 -N=CR<sub>1</sub>-,

28 -CR<sub>1</sub>=N-,

29 -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n'</sub>- where n' is an integer having the value 0 - 5,

30 -CO-NR<sub>1</sub>-,

31 -CS-NR<sub>1</sub>-,



1            $-\text{NR}_1-\text{CO},$   
 2            $-\text{NR}_1-\text{CS},$   
 3            $-\text{COO}-,$   
 4            $-\text{OCO}-;$   
 5            $-\text{CSO}-;$   
 6            $-\text{OCS}-;$   
 7            $-\text{CO}-\text{CR}_1=\text{CR}_1-;$

8            $\text{R}_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I,  $\text{CF}_3$ , fluoro  
 9 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or  
 10 alkylthio of 1 to 6 carbons;

11           $\text{R}_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

12          m is an integer having the value of 0 - 3;

13          o is an integer having the value of 0 - 4;

14          Y is a phenyl or naphthyl group, or heteroaryl selected from a group  
 15 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 16 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 17 groups being optionally substituted with one or two  $\text{R}_2$  groups, or

18          when Z is  $-(\text{CR}_1=\text{CR}_1)_n-$  and n' is 3, 4 or 5 then Y represents a  
 19 direct valence bond between said  $(\text{CR}_2=\text{CR}_2)_n$  group and B;

20          A is  $(\text{CH}_2)_q$  where q is 0-5, lower branched chain alkyl having  
 21 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons  
 22 and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple  
 23 bonds;

24          B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
 25  $\text{COOR}_8$ ,  $\text{CONR}_9\text{R}_{10}$ ,  $-\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{OR}_{11}$ ,  $\text{CH}_2\text{OCOR}_{11}$ , CHO,  
 26  $\text{CH}(\text{OR}_{12})_2$ ,  $\text{CHOR}_{13}\text{O}$ ,  $-\text{COR}_7$ ,  $\text{CR}_7(\text{OR}_{12})_2$ ,  $\text{CR}_7\text{OR}_{13}\text{O}$ , or  $\text{Si}(\text{C}_{1-6}\text{alkyl})_3$ ,  
 27 where  $\text{R}_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 28 carbons,  $\text{R}_8$  is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl  
 29 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 30 10 carbons, or  $\text{R}_8$  is phenyl or lower alkylphenyl,  $\text{R}_9$  and  $\text{R}_{10}$   
 31 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a

cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is divalent alkyl radical of 2-5 carbons, and

$R_{18}$  is alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, or the two  $R_{18}$  groups jointly form a ring having a total of 3 to 6 carbons, or the two  $X_2R_{18}$  groups jointly symbolize an oxo (=O) or a thio (=S) function, or each of the two  $X_2R_{18}$  groups is H;

22. A compound in accordance with Claim 21 wherein Y is selected from the group consisting of phenyl, naphthyl, pyridyl, thienyl and furyl.

23. A compound in accordance with Claim 22 wherein Y is phenyl.

24. A compound in accordance with Claim 22 wherein Y is naphthyl.

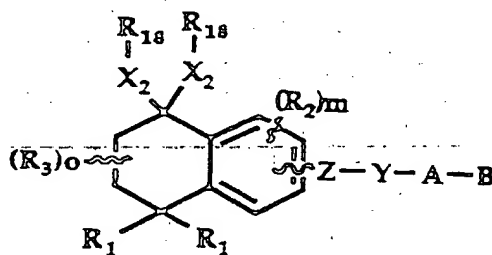
25. A compound in accordance with Claim 21 where n is 1.

26. A compound in accordance with Claim 21 where Z is selected from the groups consisting of  $-(CR_1=CR_1)_n-$ ,  $-N=N-$ ,  $-CO-CR_1=CR_1-$ ,  $-COO-$ , and  $-CONH-$  where n' is 0, 1, or 3 with the proviso that when n' is 3 then Y represents a direct valence bond between the  $-(CR_1=CR_1)_n-$  group and the -A-B group.

27. A compound in accordance with Claim 21 where A is  $(CH_2)_q$ .

28. A compound in accordance with Claim 21 where B is COOH or a pharmaceutically acceptable salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

29. A compound of the formula



- 1 where  $R_1$  is independently H or alkyl of 1 to 6 carbons;  
 2  $X_2$  is S or O;  
 3 Z is  $-N=N-$ ,  
 4  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 3,  
 5  $-CO-NH-$ ,  
 6  $-COO-$ ,  
 7  $-CO-CR_1=CR_1-$ ;  
 8  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons;  
 9  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;  
 10  $m$  is an integer having the value of 0 - 3;  
 11  $o$  is an integer having the value of 0 - 4;  
 12 Y is phenyl, naphthyl, pyridyl or thienyl with the proviso that when  $n'$   
 13 is 3 then Y represents a direct valence bond between the Z and A-B  
 14 groups;  
 15 A is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having 3-6  
 16 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1  
 17 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;  
 18 B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
 19  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  
 20  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
 21 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 22 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 23 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 24 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
 25 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 26 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 27 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 28 divalent alkyl radical of 2-5 carbons, and  
 29  $R_{18}$  is alkyl, the two  $X_2-R_{18}$  groups jointly symbolize an oxo ( $=O$ )  
 30 group or the two  $R_{18}$  groups jointly symbolize an alkenyl bridge or 2 to  
 31 5 carbons, or each of the two  $X_2R_{18}$  groups is H.

1 30. A compound in accordance with Claim 29 where Y is phenyl.

2 31. A compound in accordance with Claim 29 where Y is  
3 naphthyl.

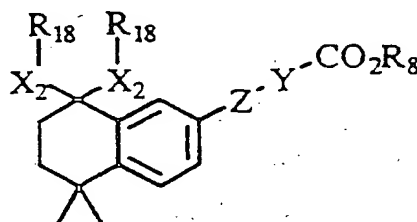
4 32. A compound in accordance with Claim 29 where A is  $(CH_2)_q$   
5 where q is 0 and where B is COOH or a pharmaceutically acceptable  
6 salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

7 33. A compound in accordance with Claim 29 where the two  $X_2$ -  
8  $R_{18}$  groups jointly symbolize an oxo ( $=O$ ) group.

9 34. A compound in accordance with Claim 29 where the two  $X_2$ -  
10  $R_{18}$  groups jointly symbolize an alkenyl bridge.

11 35. A compound in accordance with Claim 29 where each of the  
12 two  $X_2$ - $R_{18}$  groups is H.

13 36. A compound of the formula



20 where Z is  $-CH=CH$ ,  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$ ,  
21  $-N=N-$ ,  $CONH$ ,  $COO$ ;

22 Y is phenyl or when Z is  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$  then  
23 Y represents a direct valence bond between Z and  $CO_2R_8$ ;

24  $X_2$  is S or O;

25  $R_{18}$  is alkyl, the two  $X_2$ - $R_{18}$  groups jointly symbolize an oxo ( $=O$ )  
26 group or the two  $R_{18}$  groups jointly symbolize an alkenyl bridge, or  
27 each of the two  $X_2R_{18}$  groups is H.

28  $R_8$  is hydrogen or lower alkyl.

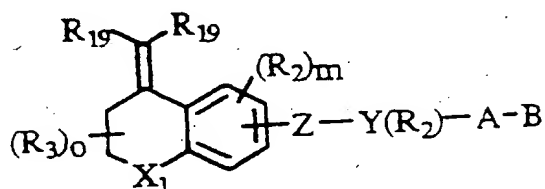
29 37. A compound in accordance with Claim 36 where the two  $X_2$ -  
30  $R_{18}$  groups jointly symbolize an oxo ( $=O$ ) group.

31 38. A compound in accordance with Claim 36 where Y is phenyl.

39. A compound in accordance with Claim 36 where Y is naphthyl.

40. A compound in accordance with Claim 36 where  $R_8$  is H or ethyl.

41. A compound of the formula



wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to 6 carbons, and  $n$  is an integer between 0 and 2;

Z is

- N=N-,
- N(O)=N-,
- N=N(O)-,
- N=CR<sub>1</sub>-,
- CR<sub>1</sub>=N,
- (CR<sub>1</sub>=CR<sub>1</sub>)<sub>n'</sub>- where  $n'$  is an integer having the value 0 - 5,
- CO-NR<sub>1</sub>-,
- CS-NR<sub>1</sub>-,
- NR<sub>1</sub>-CO,
- NR<sub>1</sub>-CS,
- COO-,
- OCO-;
- CSO-;
- OCS-;
- CO-CR<sub>1</sub>=CR<sub>1</sub>-;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or

1 alkylthio of 1 to 6 carbons;

2  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

3  $m$  is an integer having the value of 0 - 3;

4  $o$  is an integer having the value of 0 - 4;

5  $Y$  is a phenyl or naphthyl group, or heteroaryl selected from a group  
6 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
7 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl  
8 groups being optionally substituted with one or two  $R_2$  groups, or

9 when  $Z$  is  $-(CR_1=CR_1)_n-$  and  $n'$  is 3, 4 or 5 then  $Y$  represents a  
10 direct valence bond between said  $(CR_2=CR_2)_n$  group and  $B$ ;

11  $A$  is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having  
12 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons  
13 and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple  
14 bonds;

15  $B$  is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
16  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  $CHO$ ,  
17  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
18 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
19 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
20 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
21 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
22 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
23 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
24 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
25 divalent alkyl radical of 2-5 carbons, and

26  $R_{19}$  is independently hydrogen, alkyl of 1 to 10 carbons,

27 fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons

28 and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to

29 3 triple bonds, carbocyclic aryl selected from the group consisting of

30 phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 -$

31  $C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl; heteroaryl selected from the group

consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two  $R_2$  groups, further  $R_{19}$  is independently CN, CHO,  $\text{CH}(\text{OR}_{12})_2$ ,  $\text{CHOR}_{13}\text{O}$ ,  $(\text{CH}_2)_p\text{CO}_2\text{H}$ ,  $(\text{CH}_2)_p\text{CO}_2\text{R}_8$ ,  $(\text{CH}_2)_p\text{CH}_2\text{OH}$ ,  $(\text{CH}_2)_p\text{CH}_2\text{OR}_{11}$ ,  $(\text{CH}_2)_p\text{CH}_2\text{OCOR}_{11}$ , where  $p$  is an integer between 0 to 10, or the two  $R_{19}$  groups jointly represent 3 to 8 methylene groups which together with the alkylidene carbon complete a ring, the ring optionally containing 1 to 2 double bonds and the ring being optionally substituted with 1 or 2  $R_2$  groups.

42. A compound in accordance with Claim 41 wherein  $Y$  is selected from the group consisting of phenyl, naphthyl, pyridyl, thienyl and furyl.

43. A compound in accordance with Claim 42 wherein  $Y$  is phenyl.

44. A compound in accordance with Claim 42 wherein  $Y$  is naphthyl.

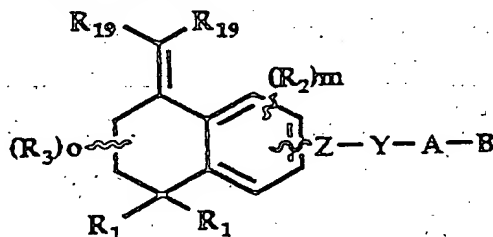
45. A compound in accordance with Claim 41 where  $n$  is 1.

46. A compound in accordance with Claim 41 where  $Z$  is selected from the groups consisting of  $-(\text{CR}_1=\text{CR}_1)_n-$ ,  $-\text{N}=\text{N}-$ ,  $-\text{CO}-\text{CR}_1=\text{CR}_1-$ ,  $-\text{COO}-$ , and  $-\text{CONH}-$  where  $n$  is 0, 1, or 3 with the proviso that when  $n$  is 3 then  $Y$  represents a direct valence bond between the  $-(\text{CR}_1=\text{CR}_1)_n-$  group and the  $-A-B$  group.

47. A compound in accordance with Claim 41 where  $A$  is  $(\text{CH}_2)_q$ .

48. A compound in accordance with Claim 41 where  $B$  is  $\text{COOH}$  or a pharmaceutically acceptable salt thereof,  $\text{COOR}_8$ , or  $\text{CONR}_9\text{R}_{10}$ .

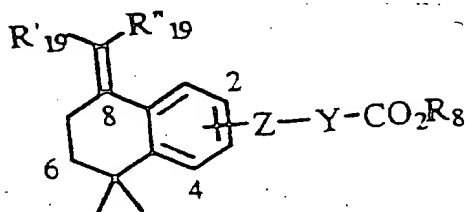
49. A compound of the formula



- 1 where  $R_1$  is independently H or alkyl of 1 to 6 carbons;  
 2 Z is  $-N=N-$ ,  
 3  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 3,  
 4  $-CO-NH-$ ,  
 5  $-COO-$ ,  
 6  $-CO-CR_1=CR_1-$ ;  
 7  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons;  
 8  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;  
 9  $m$  is an integer having the value of 0 - 3;  
 10  $o$  is an integer having the value of 0 - 4;  
 11 Y is phenyl, naphthyl, pyridyl or thienyl with the proviso that when  $n'$   
 12 is 3 then Y represents a direct valence bond between the Z and A-B  
 13 groups;  
 14 A is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having 3-6  
 15 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1  
 16 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;  
 17 B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
 18  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  
 19  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,  
 20 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 21 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 22 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 23 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
 24 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 25 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 26 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 27 divalent alkyl radical of 2-5 carbons;  
 28  $R_{19}$  is independently hydrogen, alkyl of 1 to 10 carbons, carbocyclic  
 29 aryl selected from the group consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl,  
 30  $(CH_2)_pCO_2R_8$ ,  $(CH_2)_pCO_2H$  where  $p$  is an integer between 0 to 10, or  
 31 the two  $R_{19}$  groups jointly represent 3 to 8 methylene groups which



- 1 together with the alkylidene carbon complete a ring.
- 2 50. A compound in accordance with Claim 49 where Y is phenyl.
- 3 51. A compound in accordance with Claim 49 where Y is
- 4 naphthyl.
- 5 52. A compound in accordance with Claim 49 where A is  $(CH_2)_q$
- 6 where q is 0 and where B is COOH or a pharmaceutically acceptable
- 7 salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .
- 8 53. A compound in accordance with Claim 49 where  $R_{19}$  is lower
- 9 alkyl, or where the two  $R_{19}$  groups jointly represent 3 to 8 methylene
- 10 groups which together with the alkylidene carbon complete a ring.
- 11 54. A compound in accordance with Claim 49 where at least one
- 12 of the  $R_{19}$  groups is phenyl.
- 13 55. A compound in accordance with Claim 49 where at least one
- 14 of the  $R_{19}$  groups is COOH or  $COOR_8$ .
- 15 56. A compound of the formula



- 25 where Z is  $-CH=CH$ ,  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$ ,
- 26  $N=N-$ ,  $CO-CH=CH$ ,  $CONH$  or  $COO$ ;
- 27 Y is phenyl or when Z is  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$  then
- 28 Y represents a direct valence bond between Z and  $CO_2R_8$ ;
- 29  $R_8$  is hydrogen or lower alkyl, and
- 30  $R_{19}'$  and  $R_{19}''$  independently are H, methyl, ethyl, phenyl, COOH or
- 31  $COOR_8$ .

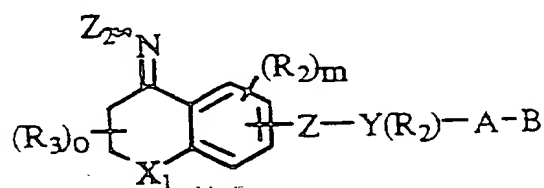
57. A compound in accordance with Claim 56 where the Z group is connected to the 2-position of the tetrahydronaphthalene ring.

58. A compound in accordance with Claim 56 where the Z group is connected to the 3-position of the tetrahydronaphthalene ring.

59. A compound in accordance with Claim 58 where Z is CO-CH=CH.

60. A compound in accordance with Claim 57 where Z is -CH=CH, C(CH<sub>3</sub>)=CH-CH=CH-C(CH<sub>3</sub>)=CH-, -N=N-, CONH, or COO.

61. A compound of the formula



wherein X<sub>1</sub> is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> where R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons, and n is an integer between 0 and 2;

Z is -N=N-,

-N(O)=N-,

-N=N(O)-,

-N=CR<sub>1</sub>-,

-CR<sub>1</sub>=N,

-(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- where n' is an integer having the value 0 - 5,

-CO-NR<sub>1</sub>-,

-CS-NR<sub>1</sub>-,

-NR<sub>1</sub>-CO,

-NR<sub>1</sub>-CS,

-COO-,

-OCO-;

1 -CSO-;

2 -OCS-;

3 -CO-CR<sub>1</sub>=CR<sub>1</sub>-;

4 R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
5 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or  
6 alkylthio of 1 to 6 carbons;

7 R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;

8 m is an integer having the value of 0 - 3;

9 o is an integer having the value of 0 - 4;

10 Y is a phenyl or naphthyl group, or heteroaryl selected from a group  
11 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
12 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
13 groups being optionally substituted with one or two R<sub>2</sub> groups, or

14 when Z is -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- and n' is 3, 4 or 5 then Y represents a  
15 direct valence bond between said (CR<sub>2</sub>=CR<sub>2</sub>)<sub>n</sub> group and B;

16 A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl having  
17 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons  
18 and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple  
19 bonds;

20 B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
21 COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
22 CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or Si(C<sub>1-6</sub>alkyl)<sub>3</sub>,  
23 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
24 carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl  
25 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
26 10 carbons, or R<sub>8</sub> is phenyl or lower alkylphenyl, R<sub>9</sub> and R<sub>10</sub>  
27 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
28 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R<sub>11</sub> is  
29 lower alkyl, phenyl or lower alkylphenyl, R<sub>12</sub> is lower alkyl, and R<sub>13</sub> is  
30 divalent alkyl radical of 2-5 carbons, and

31 Z<sub>2</sub> is OR<sub>1</sub> or OR<sub>18</sub> where R<sub>18</sub> is phenyl, benzyl, lower alkyl or lower

1 alkoxy substituted phenyl, or  $Z_2$  is  $OSi(R_2)_3$ ,  $OCOR_{14}$ ,  
 2  $OC(R_{15})(R_{16})X_2R_{17}$ ,  $N(R_{14})_2$ ,  $NHCON(R_{14})_2$ ,  $NHCSN(R_{14})_2$ , where  $X_2$  is  
 3 O or S;  $R_{14}$  is hydrogen, alkyl of 1 to 10 carbons, alkenyl of 2 to 10  
 4 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons  
 5 and 1 to 3 triple bonds, carbocyclic aryl selected from the group  
 6 consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl, naphthyl,  $C_1 -$   
 7  $C_{10}$ -alkylnaphthyl, phenyl- $C_1 - C_{10}$ alkyl, naphthyl- $C_1 - C_{10}$ alkyl;  $R_{15}$  and  
 8  $R_{16}$  are hydrogen or lower alkyl of 1 to 6 carbons,  $R_{17}$  is lower alkyl of 1  
 9 to 6 carbons, or  $R_{16}$  and  $R_{17}$  jointly form a ring having a total of 4 to 5  
 10 carbons and the  $X_2$  heteroatom.

11 **62.** A compound in accordance with Claim 61 wherein Y is  
 12 selected from the group consisting of phenyl, naphthyl, pyridyl, thienyl  
 13 and furyl.

14 **63.** A compound in accordance with Claim 62 wherein Y is phenyl.  
 15

16 **64.** A compound in accordance with Claim 62 wherein Y is  
 17 naphthyl.

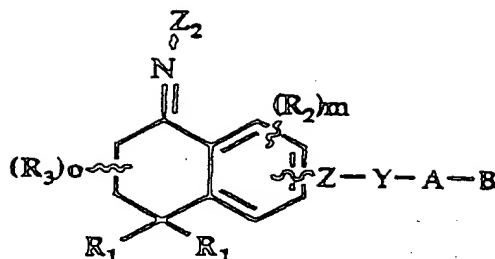
18 **65.** A compound in accordance with Claim 61 where n is 1.

19 **66.** A compound in accordance with Claim 61 where Z is selected  
 20 from the groups consisting of  $-(CR_1=CR_1)_n-$ ,  $-N=N-$ ,  $-CO-CR_1=CR_1-$ ,  
 21  $COO-$ , and  $-CONH-$  where n' is 0, 1, or 3 with the proviso that when  
 22 n' is 3 then Y represents a direct valence bond between the  
 23  $-(CR_1=CR_1)_n-$  group and the -A-B group.

24 **67.** A compound in accordance with Claim 61 where A is  $(CH_2)_q$ .

25 **68.** A compound in accordance with Claim 61 where B is  $COOH$   
 26 or a pharmaceutically acceptable salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

27 **69.** A compound of the formula  
 28  
 29  
 30  
 31



where  $R_1$  is independently H or alkyl of 1 to 6 carbons;

Z is  $-N=N-$ ,

$-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 3,

$-CO-NH-$ ,

$-COO-$ ,

$-CO-CR_1=CR_1-$ ;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons;

$R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

$m$  is an integer having the value of 0 - 3;

$o$  is an integer having the value of 0 - 4;

Y is phenyl, naphthyl, pyridyl or thienyl with the proviso that when  $n'$  is 3 then Y represents a direct valence bond between the Z and A-B groups;

A is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ , where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5

carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$  independently are hydrogen, an alkyl group of 1 to 10 carbons, or a

1 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 2 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 3 divalent alkyl radical of 2-5 carbons, and

4  $Z_2$  is  $OR_{11}$ ,  $OCOR_{14}$ ,  $OC(R_{15})(R_{16})OR_{17}$ ,  $N(R_{14})_2$ ,  $NHCON(R_{14})_2$ ,  
 5  $NHCSN(R_{14})_2$ , where  $R_{14}$  is hydrogen, alkyl of 1 to 10 carbons,  $R_{15}$  and  
 6  $R_{16}$  are hydrogen or lower alkyl of 1 to 6 carbons,  $R_{17}$  is lower alkyl of 1  
 7 to 6 carbons, or  $R_{15}$  and  $R_{17}$  jointly form a ring having a total of 4 to 5  
 8 carbons and the O heteroatom.

9 70. A compound in accordance with Claim 69 where  $Z_2$  is  $OR_{11}$ ,  
 10  $OCOR_{14}$  or  $OC(R_{15})(R_{16})OR_{17}$ .

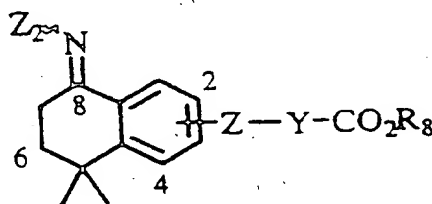
11 71. A compound in accordance with Claim 69 where Y is phenyl.

12 72. A compound in accordance with Claim 69 where Y is  
 13 naphthyl.

14 73. A compound in accordance with Claim 69 where A is  $(CH_2)_q$   
 15 where q is 0 and where B is COOH or a pharmaceutically acceptable  
 16 salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

17 74. A compound in accordance with Claim 69 where  $Z_2$  is  $OR_{11}$ .

18 75. A compound of the formula



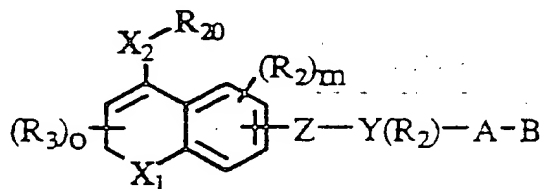
28 where Z is  $-CH=CH-$ ,  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$ , -

29  $N=N-$ ,  $CO-CH=CH-$ ,  $CONH-$  or  $COO-$ ;

30 Y is phenyl or when Z is  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$  then

31 Y represents a direct valence bond between Z and  $CO_2R_8$ .

- 1  $R_8$  is hydrogen or lower alkyl, and  $Z_2$  is OH, or O-lower alkyl.
- 2 76. A compound in accordance with Claim 75 where the Z group
- 3 is connected to the 2-position of the tetrahydronaphthalene ring.
- 4 77. A compound in accordance with Claim 75 where the Z group
- 5 is connected to the 3-position of the tetrahydronaphthalene ring.
- 6 78. A compound in accordance with Claim 77 where Z is CO-
- 7 CH=CH.
- 8 99. A compound in accordance with Claim 76 where Z is -
- 9 CH=CH,  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$ ,  $-N=N-$ , CONH, or
- 10 COO.
- 11 80. A compound in accordance with Claim 75 where  $R_8$  is H or
- 12 ethyl.
- 13 81. A compound of the formula



23 wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to

24 6 carbons, and  $n$  is an integer between 0 and 2;

25 Z is  $-N=N-$ ,

26  $-N(O)=N-$ ,

27  $-N=N(O)-$ ,

28  $-N=CR_1-$ ,

29  $-CR_1=N$ ,

30  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

31  $-CO-NR_1-$ ,

1           -CS-NR<sub>1</sub>-,  
 2           -NR<sub>1</sub>-CO,  
 3           -NR<sub>1</sub>-CS,  
 4           -COO-,  
 5           -OCO-;  
 6           -CSO-;  
 7           -OCS-;  
 8           -CO-CR<sub>1</sub>=CR<sub>1</sub>-;

9           R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
 10 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or  
 11 alkylthio of 1 to 6 carbons;

12          R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;

13          m is an integer having the value of 0 - 3;

14          o is an integer having the value of 0 - 3;

15          Y is a phenyl or naphthyl group, or heteroaryl selected from a group  
 16 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 17 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl  
 18 groups being optionally substituted with one or two R<sub>2</sub> groups, or

19          when Z is -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- and n' is 3, 4 or 5 then Y represents a  
 20 direct valence bond between said (CR<sub>2</sub>=CR<sub>2</sub>)<sub>n</sub> group and B;

21          A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl having  
 22 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons  
 23 and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple  
 24 bonds;

25          B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
 26 COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
 27 CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or Si(C<sub>1-6</sub>alkyl)<sub>3</sub>,  
 28 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 29 carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
 30 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 31 10 carbons, or R<sub>8</sub> is phenyl or lower alkylphenyl, R<sub>9</sub> and R<sub>10</sub>



1 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 2 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 3 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 4 divalent alkyl radical of 2-5 carbons;

5  $X_2$  is O, S, SO or  $SO_2$ , and

6  $R_{20}$  is  $Si(C_{1-6}alkyl)_3$ ,  $R_{14}$ ,  $COR_{14}$ ,  $SO_2R_{21}$ , where  $R_{14}$  is hydrogen, alkyl  
 7 of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double  
 8 bond, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbocyclic  
 9 aryl selected from the group consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl,  
 10 naphthyl,  $C_1 - C_{10}$ -alkylnaphthyl, phenyl- $C_1 - C_{10}$ alkyl, naphthyl- $C_1 -$   
 11  $C_{10}$ alkyl, or  $R_{20}$  is hydroxyalkyl, aminoalkyl or thioalkyl having 1 to 10  
 12 carbons; and  $R_{21}$  is alkyl of 1 to 10 carbons, fluoroalkyl of 1 to 10  
 13 carbons, or carbocyclic aryl selected from the group consisting of  
 14 phenyl,  $C_1 - C_{10}$ -alkylphenyl and phenyl- $C_1 - C_{10}$ alkyl.

15 **82.** A compound in accordance with Claim 81 wherein Y is  
 16 selected from the group consisting of phenyl, naphthyl, pyridyl, thienyl  
 17 and furyl.

18 **83.** A compound in accordance with Claim 82 wherein Y is phenyl.

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 20 **84.** A compound in accordance with Claim 82 wherein Y is  
 21 naphthyl.

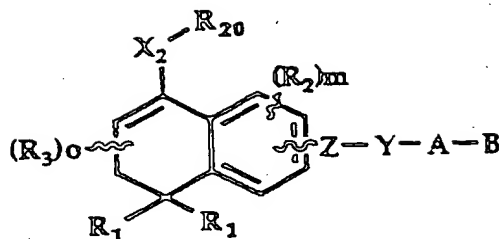
22 **85.** A compound in accordance with Claim 81 where n is 1.

23 **86.** A compound in accordance with Claim 81 where Z is selected  
 24 from the groups consisting of  $-(CR_1=CR_1)_n-$ ,  $-N=N-$ ,  $-CO-CR_1=CR_1-$ ,  
 25  $COO-$ , and  $-CONH-$  where n' is 0, 1, or 3 with the proviso that when  
 26 n' is 3 then Y represents a direct valence bond between the  
 27  $-(CR_1=CR_1)_n-$  group and the -A-B group.

28 **87.** A compound in accordance with Claim 81 where A is  $(CH_2)_q$ .

29 **88.** A compound in accordance with Claim 81 where B is COOH  
 30 or a pharmaceutically acceptable salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

31 **89.** A compound of the formula



where  $R_1$  is independently H or alkyl of 1 to 6 carbons;

$X_2$  is O, S, SO or  $SO_2$ ;

Z is  $-N=N-$ ,

$-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 3,

$-CO-NH-$ ,

$-COO-$ ,

$-CO-CR_1=CR_1-$ ;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons;

$R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

$m$  is an integer having the value of 0 - 3;

$o$  is an integer having the value of 0 - 4;

Y is phenyl, naphthyl, pyridyl or thienyl with the proviso that when  $n'$  is 3 then Y represents a direct valence bond between the Z and A-B groups;

A is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,

$CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ ,

where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5

carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl

where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to

1 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
 2 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 3 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 4 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 5 divalent alkyl radical of 2-5 carbons, and

6  $R_{20}$  is hydrogen, trialkylsilyl of 1 to 10 carbons in each alkyl group,  
 7 alkyl of 1 to 10 carbons, fluoroalkyl of 1 to 10 carbons, carbocyclic aryl  
 8 selected from the group consisting of phenyl,  $C_1 - C_{10}$ -alkylphenyl, or  
 9  $R_{20}$  is  $SO_2$ alkyl of 1 to 10 carbons, or  $SO_2$ fluoroalkyl of 1 to 10 carbons.

10 90. A compound in accordance with Claim 89 where Y is phenyl.

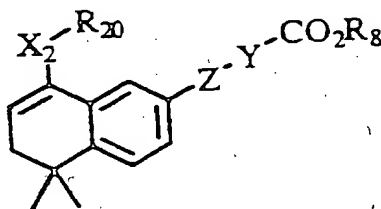
11 91. A compound in accordance with Claim 89 where Y is  
 12 naphthyl.

13 92. A compound in accordance with Claim 89 where A is  $(CH_2)_q$ ,  
 14 where q is 0 and where B is COOH or a pharmaceutically acceptable  
 15 salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

16 93. A compound in accordance with Claim 89 where  $X_2$  is O.

17 94. A compound in accordance with Claim 89 where  $X_2$  is S, SO  
 18 or  $SO_2$ .

19 95. A compound of the formula



30 where Z is  $-CH=CH-$ ,  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$ ,  
 31  $N=N-$ ,  $CONH-$ , or  $COO-$ ;

1 Y is phenyl or when Z is  $C(CH_3)=CH-CH=CH-C(CH_3)=CH-$  then

2 Y represents a direct valence bond between Z and  $CO_2R_8$ ;

3  $X_2$  is O, S, SO or  $SO_2$ ;

4  $R_8$  is hydrogen or lower alkyl, and

5  $R_{20}$  is alkyl of 1 to 10 carbons, phenyl, trimethylsilyl or  $SO_2CF_3$ .

6 96. A compound in accordance with Claim 95 where  $X_2$  is O.

7 97. A compound in accordance with Claim 95 where  $X_2$  is S, SO

8 or  $SO_2$ .

9 98. A compound in accordance with Claim 97 where  $R_{20}$  is ethyl

10 or phenyl.

11 99. A compound in accordance with Claim 96 where  $R_{20}$  is

12  $SO_2CF_3$ .

13 100. A compound in accordance with Claim 96 where  $R_{20}$  is

14 trimethylsilyl.

15 101. A compound of the formula

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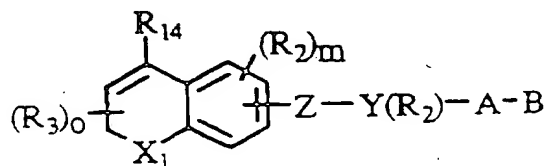
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wherein  $X_1$  is  $[C(R_1)_2]_n$  where  $R_1$  is independently H or alkyl of 1 to 6 carbons, and  $n$  is an integer between 0 and 2;

25 Z is  $-N=N-$ ,

26  $-N(O)=N-$ ,

27  $-N=N(O)-$ ,

28  $-N=CR_1-$ ,

29  $-CR_1=N-$ ,

30  $-(CR_1=CR_1)_{n'}$  where  $n'$  is an integer having the value 0 - 5,

31  $-CO-NR_1-$ ,

1           -CS-NR<sub>1</sub>-,  
 2           -NR<sub>1</sub>-CO,  
 3           -NR<sub>1</sub>-CS,  
 4           -COO-,  
 5           -OCO-;  
 6           -CSO-;  
 7           -OCS-;  
 8           -CO-CR<sub>1</sub>=CR<sub>1</sub>-;

9       R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>, fluoro  
 10 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or  
 11 alkylthio of 1 to 6 carbons;

12       R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;

13       m is an integer having the value of 0 - 3;

14       o is an integer having the value of 0 - 3;

15       Y is a phenyl or naphthyl group, or heteroaryl selected from a group  
 16 consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
 17 thiazolyl, oxazolyl, imidazolyl and pyrrolizyl, said phenyl and heteroaryl  
 18 groups being optionally substituted with one or two R<sub>2</sub> groups, or

19       when Z is -(CR<sub>1</sub>=CR<sub>1</sub>)<sub>n</sub>- and n' is 3, 4 or 5 then Y represents a  
 20 direct valence bond between said (CR<sub>2</sub>=CR<sub>2</sub>)<sub>n</sub> group and B;

21       A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl having  
 22 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons  
 23 and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple  
 24 bonds;

25       B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  
 26 COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
 27 CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or Si(C<sub>1-6</sub>alkyl)<sub>3</sub>,  
 28 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
 29 carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl  
 30 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
 31 10 carbons, or R<sub>8</sub> is phenyl or lower alkylphenyl, R<sub>9</sub> and R<sub>10</sub>

1 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
 2 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
 3 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
 4 divalent alkyl radical of 2-5 carbons;, and

5  $R_{14}$  is  $(R_{15})_r$ -substituted alkyl of 1 - 6 carbons,  $(R_{15})_r$ -substituted  
 6 alkenyl of 1 - 6 carbons and 1 or 2 double bonds,  $(R_{15})_r$ -substituted  
 7 alkynyl of 1 - 6 carbons and 1 or 2 triple bonds,  $(R_{15})_r$ -phenyl,  
 8  $(R_{15})_r$ -naphthyl,  $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3  
 9 heteroatoms selected from the group consisting of O, S and N, or  $R_{14}$  is  
 10  $(CH_2)_pCO_2H$  or  $(CH_2)_pCO_2R_8$  where  $p$  is integer between 0 to 10,  $r$  is an  
 11 integer having the values of 0 - 5, and

12  $R_{15}$  is independently H, F, Cl, Br, I,  $NO_2$ ,  $N(R_8)_2$ ,  $N(R_8)COR_8$ ,  
 13  $NR_8CON(R_8)_2$ , OH,  $OCOR_8$ ,  $OR_8$ , CN, COOH,  $COOR_8$  an alkyl group  
 14 having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10  
 15 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double  
 16 bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or  
 17 a trialkylsilyl or trialkylsilyloxy group where the alkyl groups  
 18 independently have 1 to 6 carbons.

19 **102.** A compound in accordance with Claim 101 wherein Y is  
 20 selected from the group consisting of phenyl, naphthyl, pyridyl, thienyl  
 21 and furyl.

22 **103.** A compound in accordance with Claim 102 wherein Y is  
 23 phenyl.

24 **104.** A compound in accordance with Claim 102 wherein Y is  
 25 naphthyl.

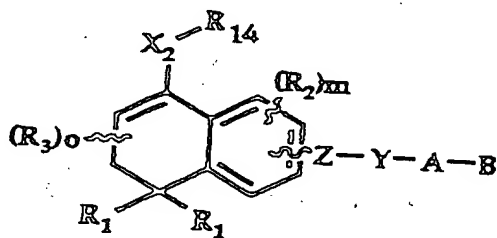
26 **105.** A compound in accordance with Claim 101 where  $n$  is 1.

27 **106.** A compound in accordance with Claim 101 where Z is  
 28 selected from the groups consisting of  $-(CR_1=CR_1)_{n'}$ ,  $-N=N-$ ,  $-CO-$   
 29  $CR_1=CR_1-$ ,  $-COO-$ , and  $-CONH-$  where  $n'$  is 0, 1, or 3 with the  
 30 proviso that when  $n'$  is 3 then Y represents a direct valence bond  
 31 between the  $-(CR_1=CR_1)_{n'}$  group and the -A-B group.

107. A compound in accordance with Claim 101 where A is  $(CH_2)_q$ .

108. A compound in accordance with Claim 101 where B is COOH or a pharmaceutically acceptable salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

109. A compound of the formula



where  $R_1$  is independently H or alkyl of 1 to 6 carbons;

Z is  $-N=N-$ ,

$-(CR_1=CR_1)_n-$  where  $n$  is an integer having the value 0 - 3,

$-CO-NH-$ ,

$-COO-$ ,

$-CO-CR_1=CR_1-$ ;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons;

$R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

$m$  is an integer having the value of 0 - 3;

$o$  is an integer having the value of 0 - 4;

Y is phenyl, naphthyl, pyridyl or thienyl with the proviso that when  $n$  is 3 then Y represents a direct valence bond between the Z and A-B groups;

A is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or-2 double-bonds, alkynyl having 2-6-carbons and 1 or-2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ , CHO,  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or  $Si(C_{1-6}alkyl)_3$ .

1 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5  
2 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl  
3 where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to  
4 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$   
5 independently are hydrogen, an alkyl group of 1 to 10 carbons, or a  
6 cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is  
7 lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is  
8 divalent alkyl radical of 2-5 carbons, and

9  $R_{14}$  is alkyl of 1 - 6 carbons,  $CH_2COOH$ ,  $CH_2COOR_8$  or  
10  $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3 heteroatoms  
11 selected from the group consisting of O, S and N, r is an integer having  
12 the values of 0 - 5, and

13  $R_{15}$  is independently H, F, Cl, Br, I,  $NO_2$ ,  $N(R_8)_2$ , OH,  $OCOR_8$ ,  $OR_8$ ,  
14 CN, COOH,  $COOR_8$ , an alkyl group having 1 to 10 carbons, or fluoro  
15 substituted alkyl group having 1 to 10 carbons.

16 110. A compound in accordance with Claim 109 where Y is phenyl.

17 111. A compound in accordance with Claim 109 where Y is  
18 naphthyl.

19 112. A compound in accordance with Claim 109 where A is  $(CH_2)_q$   
20 where q is 0 and where B is COOH or a pharmaceutically acceptable  
21 salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

22 113. A compound in accordance with Claim 109 where the  $R_{14}$   
23 group is 2-thienyl or 2-thiazolyl.

24 114. A compound in accordance with Claim 109 where the  $R_{14}$   
25 group is tertiary butyl.

26 115. A compound in accordance with Claim 109 where the  $R_{14}$   
27 group is  $CH_2COOH$  or  $CH_2COOR_8$ .

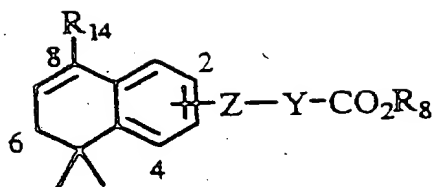
28 116. A compound of the formula

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where Z is  $-\text{CH}=\text{CH}$ ,  $\text{C}(\text{CH}_3)=\text{CH}-\text{CH}=\text{CH}-\text{C}(\text{CH}_3)=\text{CH}-$ ,  $-\text{N}=\text{N}-$ ,  $\text{CO}-\text{CH}=\text{CH}$ ,  $\text{CONH}$ , or  $\text{COO}$ ;

Y is phenyl or when Z is  $\text{C}(\text{CH}_3)=\text{CH}-\text{CH}=\text{CH}-\text{C}(\text{CH}_3)=\text{CH}-$  then Y represents a direct valence bond between Z and  $\text{CO}_2\text{R}_8$ ,

$\text{R}_8$  is hydrogen or lower alkyl, and

$\text{R}_{14}$  is  $\text{CH}_2\text{COOR}_8$ , *t*-butyl, 2-thiazolyl or 2-thienyl.

117. A compound in accordance with Claim 116 where the Z group is connected to the 2-position of the dihydronaphthalene ring.

118. A compound in accordance with Claim 116 where the Z group is connected to the 3-position of the dihydronaphthalene ring.

119. A compound in accordance with Claim 118 where Z is  $\text{CO}-\text{CH}=\text{CH}$ .

120. A compound in accordance with Claim 117 where Z is  $-\text{CH}=\text{CH}$ ,  $\text{C}(\text{CH}_3)=\text{CH}-\text{CH}=\text{CH}-\text{C}(\text{CH}_3)=\text{CH}-$ ,  $-\text{N}=\text{N}-$ ,  $\text{CONH}$ , or  $\text{COO}$ .